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THE MEDICAL CLINICS
OF
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Volume 14 No. 1

FOREWORD

In 1929 the University of California established a Visiting Lectureship in the Medical School. Dr. Lewellys F. Barker, Emeritus Professor of Medicine of Johns Hopkins University, Baltimore, Md., was happily chosen by Dean Langley Porter as the first lecturer because of his wide experience and skill as a teacher and clinician.

Many will remember with profit and pleasure the Tuesday Clinics given by Dr. Barker in Baltimore in former years. The method of case presentation and discussion has served as a model for many followers in medical schools throughout the country, but few have been able to display such knowledge upon a clinical subject, or to express it in such a delightful manner.

During a period of four weeks, in November and December, 1929, Dr. Barker became a most active member of the Medical Faculty of the University of California, taking part in Ward Rounds and Clinicopathologic Conferences and giving Amphitheater Clinics. During this time he also spoke before the Medical Societies and shared in the life of our community.

The clinics and conferences proved so inspiring and instructive to students, teachers, and practitioners that it was agreed that they merited wider distribution. W. B. Saunders Company have kindly arranged to publish Dr. Barker's clinics as a University of California number of the Medical Clinics of North America.

William J. Kerr,
Professor of Medicine.

The University of California Medical School.

ADDRESS ON THE DANGERS OF NEGLECT OF ACCURACY IN PHYSICAL EXAMINATIONS[1]

In this city you have a number of medical men who are renowned throughout our whole country for the accuracy and expertness of their physical examinations. But, notwithstanding this fact, there are doubtless some men in practice, here, as elsewhere, who are not always as careful and thorough as they should be in the physical examination of their patients.

Clinical diagnosis is, today, a wholly different matter from that of forty years ago. When I contrast the conceptions of the diagnostic problem, the methods of accumulating data with regard to patients, and the modes of arranging them and of drawing diagnostic conclusions from them that prevailed when I graduated in 1890 with those that are made use of by our better diagnosticians of the present time, I cannot help being amazed at the great changes that have taken place. We view the problems very differently; we have entirely new methods of obtaining facts; the older methods have been considerably modified and have undergone very important extensions; and from the facts gathered we are now able to draw inferences that before were wholly impossible. During these past four decades a veritable revolution in diagnostic procedures has been going on under our eyes!

The diagnostic problems that confront us today involve more than the naming of the maladies and the recognition of their anatomical substrata; they include the making of pathologic-physiologic diagnoses, the discovery of etiologic factors, the determination of the series of events that have intervened between the action of causes and their later results (that is to say, the detection of the several links in the pathogenetic chains), the separation of constitutional from environmental factors in the origin of inadequacies of biological adjustments, the reactions of human persons, as a whole, to the situations in which they find themselves, and the discovery of the physical, chemical, psychological and situational means that can best be employed to gain and to maintain the highest possible level of vital sufficiency of each person examined. That this represents a vast widening of our ideas of the functions of medical diagnosis, all will, I think, agree.

The technic of diagnostic studies was, of course, forced to undergo steady expansion as this evolution of our general notions of what diagnosis can and should mean progressed. Moreover, the vast increase in

[1] Address delivered by invitation before the San Francisco County Medical Society, December 10, 1929.

our knowledge of physics, chemistry, biology, psychology, anatomy, histology, physiology, pathology, bacteriology, and immunology made necessary the invention of many new technical methods in order that the advances could be suitably applied to the work of garnering data concerning the patient.

Even the technic of acquiring information by means of interrogation had to be elaborated, for we could no longer be content with registration of the causes of death of the immediate family, of the diseases through which the patient had passed, and of the outstanding symptoms of which he complained; we found it important systematically to inquire into his hereditary tendencies with consideration of dominant or recessive mendelian traits as, for example, in the cases of intestinal polyposis that Dr. Alson R. Kilgore demonstrated at the San Francisco Hospital this morning. We learned, too, that by means of suitable questions we could "dig out" information that threw light upon domains that his own voluntary account would have left obscure; and we further discovered that for a proper understanding of his "make-up" it was sometimes necessary to inquire into his economic and social relationships and into the whole history of his thinking, his feeling, and his striving. Thus our anamnestic records have become markedly enriched to the advantage of our patients.

The technic of our objective methods of examination became still more expanded. It soon grew clear that there were many things to see, many things to feel, many things to hear, many things to measure that we had not even dreamed of seeing, feeling, hearing, or measuring before. Moreover, physical and chemical procedures were devised and instruments of precision were invented to make accessible to sight and touch and hearing, regions, cavities, and processes that were quite out of reach of our unaided sense organs. The clinical laboratory developed and taught us how to use color tests, how to count the different kinds of blood cells, how to examine sputum, stomach contents, urine and feces, how to recognize impairment of renal function, how to make blood cultures and serological tests, and how to determine the basal metabolic rate. The *x*-ray laboratory appeared and taught us to see and measure organs and lesions in the chest, the abdomen, and the skull, and how to detect more accurately than ever before alterations in the bones and joints of the body; thus we could measure precisely the size of the heart and depict its exact shape; we could determine the site and extent of a tuberculous, a bronchiectatic, a suppurative, or a neoplastic process in the lungs more satisfactorily than was possible by percussion alone; we could see the size and position of ulcers, diverticula, polyps, and neoplasms in the gastro-intestinal tract, and could easily detect alterations in position, in size of lumen, and in motility; we could visualize the gallbladder and ascertain how it filled and emptied; we could make gallstones and stones in the genito-urinary tract visible; we could outline internal tubes and cavities filled with iodide solution or lipiodol; and of the like,

more. The instrument-makers, responsive to medical curiosity, improved our microscopes, our ophthalmoscopes, and our laryngoscopes. The new halometer of Eves, which Dr. Cheney has shown me in use here, permits us, at a glance through it at a blood slide, to determine the average diameter of the red cells and to recognize, almost in a moment, the degree of megalocytosis that points to a pernicious anemia or a funicular myelopathy. Electrical illumination was applied to new instruments for inspection of interior parts—the bronchi, the esophagus, the stomach, the rectum and sigmoid, and the bladder.

This huge methodological expansion came with great rapidity and outgrew the capacity of medical students to learn and of practitioners to apply equally well all these new things. Today, there is no single person living who dare say that he is even acquainted with all the methods, much less assert that he can skilfully apply them all. Hence the rise of specialism—the necessity for the advent of men trained as experts in diagnostic examinations and in therapy in particular domains. You know them—for the general practitioner, formerly satisfied with the help of the general surgeon, the general internist, the specializing obstetrician and gynecologist, and the specialists in nose and throat and eyes and ears, now turns on occasion to the cardiologist, the gastro-enterologist, the urogenital surgeon, the brain surgeon, the orthopedist, the roentgenologist, the immunologist, the neuropsychiatrist, or the endocrinologist (and this by no means exhausts the list!).

As a result of all this, some general practitioners developed (with wrong) an inferiority complex, and some clinical specialists exhibited, I fear (and also with wrong), a superiority complex! Many patients were not studied by the best methods available in special domains to which their symptoms pointed; whereas some patients were examined intensively in certain special domains though others equally important in the particular instance, as well as the person, as a whole, suffered almost entire neglect. Laymen, hearing of the notable achievements of specialists, tended sometimes to desert their family physicians and to apply directly to a specialist—too often to one less needed than another.

The dangers attendant upon such action soon became apparent; then diagnosis by groups came into vogue in order that comprehensive diagnostic studies could be made of all the organs and organ systems as well as of the whole personality and a therapy adequate to all the needs of the patient planned. Properly organized and conducted such group clinics can be of great service in selected cases, especially in those that are more obscure; but, too often, through faulty organization, or through incapacity of personnel, such group diagnosis has degenerated into a disturbing polypragmaticalness—the making of an enormous number of tests (whether indicated or not) without any adequate consideration of the studies needed, or of the results that the examinations yield, and without proper integration of these results into a fully justified, well-

knit, multidimensional diagnosis in which the several components are arranged according to their relative importance for the patient!

After listening to me thus long and knowing the brief time allotted to this paper, you may think that I have forgotten the subject announced, namely, "The Dangers of Neglect of Accuracy in Physical Examinations." I shall turn to it at once, though the foregoing seemed to me to be desirable as an introduction to what follows. For I am strongly of the opinion that no matter what symptom a patient presents, no matter who examines him—be it general practitioner, specialist, or diagnostic group—that patient, in addition to and before any laboratory tests, any *x*-ray tests, or any examination in a special domain that may be made, should have a thorough general physical examination and it should be skilfully conducted. Of course, in a medical or a surgical emergency, immediate therapeutical intervention may be absolutely necessary after a size-up of the condition that may be almost momentary; one does not make a long and elaborate diagnostic survey before setting a fractured thigh, before stopping hemorrhage, before easing the pain of angina pectoris, before giving antitoxin in diphtheria, or before quieting a homicidal maniac. Our common sense and our medical experience will protect us from an error of this sort. But after an emergency has passed, the patient should be examined most carefully physically, in all regions, from head to toe, *and when he is undressed and in a good light.* For the general physical examination, competently made, is the very heart of a diagnostic study; without making it and without giving due consideration to its positive and negative findings, the anamnesis, the clinical laboratory, the *x*-ray laboratory, or the technics of the specialist may lead us far astray, helpful as any one or all of them may be *along with the results of the general physical examination* in guiding us to correct interpretations. If I were a general surgeon or a medical or surgical specialist I should be unwilling, aside from an emergency demanding immediate intervention, to undertake the treatment of a patient without first having available the results of a competent general physical exploration; if for any reason I could not make it myself, I should arrange to have someone whose technical competency I trusted, make it for me. For the choice of an anesthetic may depend upon the condition of the heart muscle, upon the degree of renal sufficiency or upon the behavioristic reactions of the patient. The compensation that is to be given to a disabled employee cannot be fairly determined without the concrete data (obtainable by physical examination) that will permit a rating board to evaluate properly the disability. Local treatment of an infectious arthritis may be of but relatively little use while a focal infection in some distant part is still active. It would be actual folly to operate on a thyroid or to atttempt extirpation of a brain tumor if the patient had a rheumatic valvular disease of the heart to which a blood-stream infection with *Streptococcus viridans* had become associated. Nor would it be wise to prescribe cas-

cara or a compound cathartic pill for constipation when a physical examination could reveal a visible and palpable rigid intestinal loop betokening intestinal obstruction. There is no advantage to be gained for a patient by submitting him to an elaborate endocrine therapy, even if he have endocrine disease, when he can be shown by physical examination to have also a cancer of the esophagus, or the rigidity of a catatonic schizophrenia, or a splenomegaly with many enlarged lymph glands that in turn might lead to the findings of a leukemic blood picture. It would scarcely be justifiable, either, to resort to exploratory laparotomy for paroxysms of severe abdominal pain without first finding out whether or not the patient's pupils react to light or whether a spastic colon can be felt. I could give a hundred other examples, but each of you can, I am sure, supplement the list given by observations of your own. What ignorance, what neglect, or what conscienceless daring must exist to permit anyone in these days to make mistakes of this sort!

In our studies of manifest disease the accurate physical examination is important enough; it is even more important for the recognition of incipient disease, of latent disease, and of signs that may be precursors of disease. Much tuberculosis is being prevented by the early recognition of an apical catarrh; many cancer deaths could be avoided if the precancerous lesions (sore lip or tongue; retracted nipple; suspicious nevi and moles, polypi in the rectum, etc.) were discovered and properly dealt with; much diabetes would fail to develop if physicians examining obese people told them that they were nineteen times more prone to develop diabetes than are people of normal weight.

But one must know how adequately to interpret the physical signs that he finds. Most consulting diagnosticians have known sounds of muscular origin to be taken for râles of tuberculous origin at the apex of the right lung; I have seen patients kept in bed for weeks because of the discovery of a soft systolic murmur over the heart when it had no serious import whatever; and you must all know of young persons who have been treated for supposedly severe renal disease when physical examination (together with studies of the urine) would have disclosed the postural defect responsible for an orthostatic albuminuria.

The danger, too, of examining only the local region of which the patient complains rather than the body as a whole would seem obvious enough. I have heard of an important patient who had long suffered from a paralysis of one arm and had been examined by many nerve specialists and other consultants without correct diagnosis until a keen diagnostician in this city, on routine physical examination, discovered a peculiar dulness at the apex of one lung, which further study proved to be due to a tumor mass pressing upon the brachial plexus; deep *x*-ray treatment gave great amelioration!

Despite the importance of avoiding any unnecessary preoccupation with the condition of the body, I am a strong supporter of the move-

ment toward periodic health examinations of the supposedly well. The experience with candidates for military service during the Great War proved their necessity for disease detection and for disease prevention. The humanitarian argument is unassailable; it is clearly our duty to do all that we can to prevent disease and suffering. We have already lengthened the span of life by a decade and a half, but this has been chiefly by salvage in infancy, childhood, and adolescence. The problem of preventing the degenerative diseases of later life has still to be solved. That much can be done to solve it has been proved by the insurance companies and by the corporate industries that have arranged for annual health examinations of policy holders and employees respectively. Here an economic argument can be added to the humanitarian appeal; for the insurance companies have made 100 per cent upon the money invested in their preventive work; and employers of industrial workers are finding that they can increase productivity and save money in other ways by paying for regular health examinations of their workers. Not many people realize that the annual cost of illness in a country amounts to about thirty dollars per head calculated for the total population!

Not long ago I had the privilege of talking to an association of railway surgeons upon the same topic that I am dealing with tonight. Railway surgeons have begun to realize the importance of regular physical examinations. I understand that railway companies are paying ever more attention to the physical examination of their employees. They would not willingly allow a man to drive an engine if he were color blind, or if he had an Argyll Robertson pupil and a positive Wassermann. Even the high officials of a railroad should be regularly examined, for persons in positions of great responsibility have often done incalculable harm to business corporations or to governments before they were recognized as sick. Such officers hold their positions because of their supposed executive ability and sound judgment. But a few spirochetes in the brain acting insidiously, or a gradual thickening of the brain arteries, or a developing tumor in the frontal lobe of the brain, may so alter the judgment of men that they may make the gravest mistakes before their colleagues suspect that they are ill, though their physicians could have detected the developing maladies, and given the warnings that might have prevented the catastrophes.

A cruiser of one of the navies during the recent war ran into a mined area of its own country though the position of this mined area was well known to the navigation officer; owing, however, to a developing dementia paralytica his calculations of the ship's course were faulty; several lives were lost and his cruiser was thrown out of commission for the next six months. Similar examples could doubtless easily be given by medical officers of the army and navy of any country.

Resort to periodic physical examinations should become general; but for men of large responsibility and for persons upon whose health the

lives and the property of many others may largely depend the practice cannot be too strongly recommended. The growth of such periodic physical examinations will throw a great burden upon the medical profession; but it is a profession that has never been afraid of work, and it will always find some way, we can feel sure, of meeting the medical needs of mankind.

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AMPHITHEATER CLINICS[1]

PRESENTATION OF A PATIENT SUFFERING FROM TYPHOID FEVER AT THE END OF THE THIRD WEEK OF THE DISEASE

Discussion of Contemporary Methods of Diagnosis, the Treatment and the Differentiation of the Typhoid Group of Diseases[2]

It will be observed that the patient before you is in a bed protected by sheets at the sides and that the doctors and nurses accompanying him are dressed in white coats. Each person who comes in contact with him disinfects the hands carefully immediately afterward. The patient is suffering from one of the group of typhoidal diseases and I may tell you at once that the diagnosis of typhus abdominalis has been made in his case, beyond doubt, by the demonstration of the presence of the *Bacillus typhosus* of Eberth in the circulating blood, as well as in the feces. The case has, of course, been promptly reported to the city health authorities.

Some twenty-five years ago when I was given the responsibility of the chair of medicine in the Johns Hopkins Medical School, we were having, every autumn, in our medical wards some 200 cases of this type of disease. I know of no more striking change, perhaps, in the incidence, in recent years, of any disease than in that of typhoid fever. Nowadays, it is often very difficult in our medical clinics in the East to find a single case of typhoid fever for teaching purposes. Professor Kerr tells me that you have had a similar experience here in San Francisco, that it is only occasionally that a patient belonging to the typhoid group of diseases enters the clinic and is available for presentation to the class. When I was in Munich last summer, Prof. Friedrich Müller, the distinguished head of the medical clinic there, told me that it was now most rare for him to find a case for discussion before his students. I feel, therefore, that we are very fortunate in having the opportunity today of presenting to you a fairly typical case of the disease.

In the old days these typhoidal cases were admitted to the general wards of our hospitals; they were not kept in special isolation wards.

[1] Dr. Barker desires to express his thanks to Professor Kerr, and all the members of the staffs of the hospitals, who left nothing undone to help him in the preparation of the material for the clinics and the clinico-pathological conferences. He is also very grateful to Miss Sturla, Miss Payne, and Miss Terry for aid with the manuscript and other help.

[2] Amphitheater Clinic, University of California Medical School, December 4, 1929.

Indeed, in the autumn of every year our public wards were crowded with cases of typhoid, often largely to the exclusion during the autumn months of patients suffering from other maladies. We could not possibly, at that time, have isolated these patients completely for our isolation ward at the Johns Hopkins Hospital was small and was designed merely for the reception of occasional cases of diphtheria, scarlet fever, and other highly contagious diseases. Nowadays, it is customary to keep typhoid patients in the isolation wards, though, as a matter of fact, there is but little danger attendant upon keeping them in the general wards, provided suitable precautions are observed. In the old days much of the teaching of internal medicine in the autumn had to be done upon patients with typhoid fever. As you probably know, if one sees a large series of typhoid patients, there will be among them instances of abdominal, renal, cardiac, pulmonary, meningeal, cerebral, periosteal, and other complications so that one can give a very good course in internal medicine in the wards upon typhoid patients alone provided they are present in sufficient numbers. I remember very well a comment made by Dr. Osler in the 'nineties, when he remarked that if one knew his typhoid fever well he could scarcely fail to know his internal medicine well.

As I have said, the incidence of this disease has undergone a tremendous decrease since the days of which I have just spoken. This is true not only of the large cities of the United States, but of all large cities in the world. In this number of the *Journal of the American Medical Association* that I am passing around, you will find an article upon the occurrence of typhoid fever in our large cities during the year 1928 and a comparison with the incidence of the disease in earlier years. You will observe that in the quinquennium, 1906–1910, there were about 35 deaths from typhoid per 100,000 of population in the city of Baltimore. In San Francisco during the same five years the mortality was somewhat less; you had about 27 deaths from typhoid per 100,000 of population. From 1910–1915 we had a mortality rate of 15.7 in Baltimore and your rate was 13.6. From 1915 to 1920 our rate had fallen to 11.8 and yours to 4.6, so your progress in the reduction of mortality from typhoid was somewhat more rapid than ours. By 1927 a very low rate of mortality could be reported from nearly all large cities in this country; in Baltimore the rate had fallen to 1.8 per 100,000 of population and your rate was down to 1.7. During the past year (1928) there was a slight increase again in the mortality rate; it reached 3.8 per 100,000 of population in Baltimore and 3.4 per 100,000 here in San Francisco. Dr. Karl F. Meyer tells me that this increase was due to milk contamination and he feels that the inspection of the process of pasteurization of milk should be more rigid than it has been. For example, on investigation of one source of milk supply which was suspected, he and his associates found that a typhoid bacillus carrier worked in the plant, and that this carrier had been touching with his fingers the cardboard sealers of the

bottles because of a defect in the machine that ordinarily closed the milk bottles automatically!

It is interesting that, despite the slight increase in many cities during 1928, there were some cities in which no typhoid deaths occurred at all and these cities, notably Duluth, Elizabeth, Lowell, New Haven, Springfield, Tacoma, Yonkers, and Youngstown were accordingly placed in an "honor list" by the *Journal*.

It would not be surprising if there were some increase in the mortality rate during this year on the Pacific Coast on account of the prolonged absence of rainfall during the summer and autumn. Experience has shown that a fall in the level of the ground water is accompanied by an increase of bacteria in the ground water and a corresponding increase in the incidence of typhoid fever.

Before entering upon a discussion of the main features of the disease, I shall ask Dr. Evelyn Anderson to give you an epitome of the history of the patient before you.

CASE HISTORY

The patient, A. L. P., single, white man, a painter, was admitted to the University of California Hospital (Service of Professor Kerr) on November 30, 1929.

His *complaints* were of fever and of daily chills for the preceding ten days.

The *past* history was practically negative except that he had been an obese man for many years and had suffered from malaria at the age of twenty-two.

The *present illness* followed a vacation in Southern California. He had gone by train to Los Angeles and to San Diego and had returned by stage through the San Joaquin Valley. During the trip he had felt exceptionally well. On the morning after his return to San Francisco (sixteen days before admission to the Hospital) he awoke in the morning with "smarting eyeballs, a feeling of weakness, a severe headache and aching all over the body." Though he went to his work despite these symptoms he was unable to continue it as he felt too ill; he returned to a hotel, in which he lives (though he takes his meals at restaurants). Three days later he began to have what he described as "cold spells" up and down his spine and, at the same time, noticed that throughout the rest of his body he felt very hot. All the symptoms that had first appeared became aggravated; he stressed especially the smarting of the eyeballs. He states that during this time his mind was hazy and that he "felt nervous and trembly." Despite his illness, however, he arose every day, went to a store and bought milk and fruit upon which he lived before coming to the Hospital.

DR. BARKER: He was more or less ambulatory then during this period?

DR. ANDERSON: Yes, he was up every day and even a week ago yesterday he came to the Clinic looking very well.

DR. BARKER: Did he drive to the Hospital, or walk, or did he come in an ambulance?

DR. ANDERSON: He came out on the street car. We found his temperature shortly after arrival to be 40 C. (about 104 F.). His pulse was 104.

DR. BARKER: That is interesting—a pulse of only 104 though his temperature was 104 F. If you should see a patient with pneumonia with a temperature of 104 F. he would have a pulse probably of 120 or 160. This relative bradycardia (contrasted with the elevation of the temperature) is very characteristic of the group of typhoidal diseases.

DR. ANDERSON: During this period he had no nausea, no vomiting, and no diarrhea; in fact, he was constipated, and he tells us that he took saline cathartics in large amounts, including Pluto water for relief of the constipation.

DR. BARKER: Despite the well-known association of this disease with lesions in the intestines, it is surprising to find how many patients are constipated at the beginning. Of course it was unwise to take purgatives as he did. It is better to relieve the constipation by enemata than by purgation but the patient was doubtless ignorant of this fact.

DR. ANDERSON: He had nosebleeds during this early period.

DR. BARKER: Epistaxis at the onset of typhoid is a very common symptom.

DR. ANDERSON: On examining him, in addition to his high fever, we found that his face was flushed and that the facial expression was rather dull. He was still complaining of headache.

DR. BARKER (to the patient): Are you still having headache?

PATIENT: No. The headache stopped two days ago.

DR. BARKER: Then he had headaches during the first fifteen days of his disease. It is very unusual to have headache last so long in typhoid. As a rule the headache stops on about the tenth day of the disease, probably owing to the cerebral intoxication. During the first week of the disease the patients are often restless, sleepless, somewhat overalert and overactive, but about the tenth day they usually begin to appear dull or sometimes a little delirious and they stop complaining of their headaches. In Baltimore, we were of the opinion that the day the headache stopped could be marked as the tenth day of the disease, but this man's headache continued, as you see, much longer. Almost all our clinical rules of this sort are subject to some exceptions!

DR. ANDERSON: The abnormal findings on physical examination were few. The pulse rate was 104, the heart sounds were somewhat feeble; the breath sounds were a little harsher and somewhat higher pitched than normal but no râles could be heard.

DR. BARKER: Were there no rhonchi or so-called dry râles?

DR. ANDERSON: No, we heard none.

DR. BARKER: That is rather surprising for one of the characteristics of the disease is the existence of a diffuse dry bronchitis during the febrile period and this bronchitis as a rule gives rise to rhonchi that are easily audible, especially over the bases. What else was found on physical examination?

DR. ANDERSON: The abdomen was found distended and felt tense, but there was no marked tenderness on palpation. There were a few reddish spots on the abdomen but the internes were not sure whether they were rose spots or not as some of them had never seen rose spots.

DR. BARKER: Internes who had never seen a rose spot—think of that! This proves how rarely the students in medical schools today have the opportunity of studying typhoid cases. In the old days one could not go through the medical wards in the autumn without seeing a large number of cases exhibiting typical typhoid roseolae. Every medical student became familiar with the appearance of rose spots and with the methods of differentiating them from other lesions that may simulate them. The distribution of the rose spots is important. They appear on the abdomen first, as a rule, and, later, they may sometimes be met with upon other parts of the trunk, only rarely upon the extremities. This primary appearance in the abdominal wall with the appearance later upon parts above and below the abdominal wall is of interest in connection with our present conception of the origin of these rose spots and of the pathogenesis of the disease in general. To this point I shall return later.

Was his spleen enlarged?

DR. ANDERSON: Yes it was very definitely increased in size, the lower pole being very palpable about 3 cm. below the costal margin. The liver was also vaguely palpable, appearing to be somewhat enlarged.

DR. BARKER: An "acute splenic tumor" (moderate enlargement of the spleen with medium or soft consistency) is a characteristic accompaniment of typhoid fever and is usually demonstrable by the eighth day of the fever and, sometimes, even earlier.

DR. ANDERSON: The physical examination was otherwise negative. There were no joint changes and no abnormal neurological findings.

On laboratory examination of the *blood* the red count was 3,760,000 with 70 per cent hemoglobin (Sahli). The white count was 4600 with 42 per cent of neutrophils and 42 per cent small mononuclears.

DR. BARKER: This man has had a rather more severe secondary anemia than we usually find at the beginning of typhoid fever. Possibly he was somewhat anemic before his infection. The leukopenia with relative lymphocytosis is characteristic of uncomplicated typhoid. Evidently the intoxication associated with typhoid fever injures in some way the leukopoiesis of the bone marrow, though the production of small mononuclears by the lymphadenoid tissues of the body does not seem to be reduced. How many monocytes or large mononuclears were found?

DR. ANDERSON: Some 14 per cent.

DR. BARKER: That is a goodly proportion of monocytes and is interesting, considering the suspected injury to the marrow. Possibly there has been a selective intoxication of the marrow with involvement, especially of the production of neutrophils rather than of monocytes.

DR. ANDERSON: The *urine* was negative except for a trace of albumin and an occasional pus cell; the specific gravity of the urine was 1.027.

DR. BARKER: When healthy persons are attacked with typhoid fever the urine is usually concentrated and of high color. Sometimes the diazo-reaction of Ehrlich is positive in the urine.

DR. ANDERSON: It was negative in this patient. A *blood culture* was made on the day of admission and it yielded a positive culture of *Bacillus typhosus*.

DR. BARKER: I am glad that the blood culture was made so promptly, for it is the best method of quickly arriving at a positive diagnosis, not only of the existence of one of the typhoidal group of diseases, but also of the particular member of the group with which you have to deal. The typhoidal group includes, as you know, infections with *Bacillus typhosus*, the *Bacillus paratyphosus* A, the *Bacillus paratyphosus* B and the *Bacilus mandschuricus*.

Not all practicing physicians seem to be familiar with the fact that *in every case of typhoid fever a blood culture made in the right way will reveal the presence of the causative bacteria in the blood on each day in which fever exists*, but the culture must be made in the right way. Usually 5 cc. of blood will suffice to allow of a positive result but in some patients 10, 15 or 20 cc. of blood may be necessary in order to detect the presence of the bacillus. In addition to the making of blood-agar plates, it is well to put some of the blood into a test tube containing bile-bouillon and to allow the tube to stand in the thermostat for twenty-four hours in order to permit of multiplication of the bacilli, after which one may make plates from the medium thus incubated for the isolation of single colonies.

It is a great satisfaction to know that by the use of these blood culture methods we can make a positive diagnosis of typhoid fever within two or three days after we see the patient. Early diagnosis is very important, not only for the differential diagnosis of the typhoid group of diseases from other acute infections, but also in order that the most suitable therapy may be promptly instituted. In this connection let me urge upon you the advisability of making blood cultures in *all* febrile infections, for you will sometimes encounter a bacteriemia when you have not suspected its existence. Thus I have known the streptococcemia that is associated with endocarditis lenta to be found only late in the disease when the presence of the *Streptococcus viridans* in the blood might easily have been demonstrated weeks or months earlier if blood cultures had been made.

DR. ANDERSON: The patient's blood serum also yielded a *positive Widal reaction;* the serum agglutinated typhoid bacillus in dilutions of 1 : 40 but it also agglutinated Gärtner's bacilli (*B. enteritidis*) in dilutions of 1 : 20. It would not agglutinate paratyphoid bacilli, nor dysentery bacilli. The macroscopical method of applying the agglutination test was employed.

DR. BARKER: A set of tubes illustrating this agglutination reaction has been set up and I will pass the test tube rack around in order that you may see the tube in which clumping has occurred and those in which there is no clumping. The Widal reaction is not nearly so useful for clinical diagnosis as is the blood culture for, as I have said, blood cultures competently made will reveal the presence of typhoid bacilli in the circulating blood on every day in which there is fever (at least during the first three weeks of the disease), whereas the Widal reaction does not become positive until about the eighth day or even later; sometimes it does not become positive until about the second or third week and, in some patients, a positive Widal reaction may never become demonstrable. It should, of course, be remembered that normal serum in high concentration may often stop the motility and cause some agglutination of the typhoid bacillus. We, therefore, do not speak of the Widal reaction as being positive unless agglutination will occur in dilutions of the serum of 1 : 50 or more. This increase in specific agglutinins in the blood in typhoid fever is due to their development as a part of the immunity reaction that follows upon typhoid infection. One must bear in mind, however, that you may meet with the so-called "group agglutination," that is to say, the serum from a typhoid patient may also agglutinate paratyphoid bacilli and similarly the serum of a paratyphoid patient may agglutinate, not only paratyphoid bacilli but also typhoid bacilli. It is, therefore, of importance to determine the increase of dilution of the serum in which each of these types of bacilli is agglutinated. There are certain special methods that may be used in well-equipped bacteriological laboratories for differentiation among the cases in which group agglutination occurs, but it would scarcely be profitable to enter upon a discussion of these special methods at this time.

Though the Widal reaction in the serum of typhoid patients usually passes off during convalescence it may last for years after the infection, so that *the demonstration of a positive Widal reaction does not indubitally indicate the existence of typhoid infection at the time the test is made.* Moreover, there appear to be certain strains of typhoid bacilli that do not agglutinate. Strange to say in certain typhoid infections no agglutination occurs in dilutions of 1 : 50 or 1 : 100 and yet in dilutions of 1 : 500 or 1 : 1000 agglutination may occur. Another important point to bear in mind in connection with the Widal reaction is that in persons who have had antityphoid inoculation earlier (say within a year) the Widal reaction may be positive. One should always inquire whether or not the patient has within nine or twelve months received preventive typhoid inoculations and if you find that such inoculations have been given a positive Widal reaction will be without value for the diagnosis of any fever that develops. I understand that this patient had not received antityphoid inoculations. With all these limitations to the interpretation of a positive Widal reaction you can readily see how relatively unimportant a positive Widal reaction is for diagnosis, in contrast with the certainty of diagnosis that the blood culture may yield.

You told me that this man's serum also agglutinated the *Bacillus enteritidis* of Gärtner, did you not?

DR. ANDERSON: Yes it did so in dilutions of 1–20.

DR. BARKER: I bring up this point for an especial reason. As I have said, a patient who has been vaccinated within a few months against typhoid and then develops a fever may yield a positive Widal reaction, even when the fever is not due to typhoid infection. But it has been found that when true typhoid fever develops in a person despite earlier preventive typhoid inoculation, the serum of the patient agglutinates not only the typhoid bacillus itself, but also the *Bacillus enteritidis* of Gärtner. This fact has been utilized as a diagnostic criterion for the recognition of mild typhoid fever after preventive inoculation.

It is often possible at the onset of typhoid fever to demonstrate the presence of typhoid bacilli in the feces and also in the urine of the patient—but not always. Were cultures made from the excreta of this patient?

DR. ANDERSON: Cultures were made from the feces, but not from the urine. Here is the plate from the feces showing many typhoid colonies.

DR. BARKER: When attempts are made to diagnose infections by bacteriological studies of feces it is necessary to make cultures upon special media that will differentiate typhoid bacilli from other bacilli belonging to the typhoidal group and from colon bacilli. For the latter purpose, the Drigalski-Conradi medium and Endo's fuchsin agar are particularly useful since typhoid colonies and colon colonies are strikingly different upon these media. A whole series of other differential media have been employed, as you will find by consultation of the newer text-books of bacteriology. Confirmation of the results obtained by differential media can be gained by the application of agglutination tests with the aid of specific immune sera.

Thanks to the development of bacteriological laboratories in connection with local Boards of Health, general practitioners can now easily obtain the aid of bacteriodiagnostic methods almost everywhere. If, however, one should be off on an expedition in the wilds, or if one be in practice in some remote rural district, far from any bacteriological laboratory, there is a method of blood culture that can easily be applied, provided one has with him a syringe for withdrawal of the blood from the vein, on the one hand, and a test tube and means of heating it on the other, as well as a microscope with oil immersion lens. It was pointed out by Gildemeister some years ago that if 2 or 3 cc. of blood from the arm vein be placed in a test tube containing 5 to 10 cc. of water (that has been heated to boiling and cooled again) and this mixture be kept in a warm place for two or three days, the appearance in this blood-and-water mixture of motile rods of the form of the typhoid bacilli makes the diagnosis of typhoid fever (or of paratyphoid) extremely probable. You may ask: Why could not one be dealing with some contamination? Well, I assume ordinary precautions would be taken in making such a culture. The examiner's hands would be carefully washed and the arm would be washed and sterilized before withdrawal of the blood. Experience has shown that cultures made with these precautions by Gildemeister's method are very reliable and that contamination with bacteria other than the typhoid or paratyphoid bacteria is extremely rare if it occur at all. The only contamination one would be likely to meet with in the circumstances would be a *Staphylococcus albus*.

When one can make the blood culture in a well-equipped clinical laboratory, it is desirable to estimate the number of colonies of typhoid bacilli present per cubic centimeter of blood. In most cases one will find about 20 colonies per cubic centimeter but as many as 50 or more per cubic centimeter have been found in severe infections. This estimation of the numbers of bacilli per cubic centimeter of blood may be of some importance as a clue to the severity of the infection, since presumably the greater the number of bacteria in the circulating blood, the severer will be the clinical phenomena. How many days would you say have elapsed since this man began to have fever?

DR. ANDERSON: I believe that this is the twenty-first day.

DR. BARKER: Well, you have proved that this man not only has been infected by bacilli belonging to the typhoid group but you have also brought the proof that the particular bacilli are not paratyphoid bacilli or colon bacilli but are the typhoid bacilli of Eberth and that some twenty-one days have elapsed since he began to have fever. In other words, he seems now to be at the beginning of the fourth week of his disease.

The *incubation period* of the disease usually lasts only from three to four days and is accompanied by mild symptoms, such as headache, pains in the legs, disinclination for exertion and poor appetite. Then the fever begins and the temperature rises in a steplike way (*stadium incrementi*) for several days. During this period, the subjective symptoms increase, and objectively the tongue becomes heavily coated, the spleen becomes palpable and the signs of a dry bronchitis appear in the lungs. It is during this stage that swelling of the mesenteric glands occurs with swelling also of

Peyer's patches and of the solitary follicles in the intestine, particularly just above the ileocecal valve.

By the end of the first week of fever the temperature has usually reached a high level and it then continues at approximately this level (with slight oscillations) during the second and third weeks of the disease (*fastigium* or *stadium acmis*). The patient complains less during this period because his consciousness has become clouded; he may seem apathetic or he may be delirious; the preliminary restlessness and anxiety have given place to a quieter state in which there is sopor and muscular relaxation. At this stage it is often difficult to get the patient to eat or to drink; usually he has to be fed by the nurse. One notices twitching of the tendons under the skin (*subsultus tendinum*) or in severe cases one may notice that the patient picks at the bed clothes (*carphologia*). This is the so-called *status typhosus* or typhoidal state. During this febrile period of the disease the rose spots appear, first on the abdomen and later, sometimes, on the chest or extremities also. Each spot lasts but a few days and then grows pale or slightly brownish in color. Rarely does one see over one dozen or two at a time though successive crops may appear. The spleen can be felt, the relative bradycardia continues, the pulse becomes dicrotic, and the urine remains dark and concentrated. Constipation may continue, or there may be slight diarrhea with the appearance of so-called "pea-soup" stools.

Complications of various sorts may set in toward the end of the fastigium; one must be on the lookout for intestinal hemorrhage or for signs of intestinal perforation and perforative peritonitis. The blood shows a secondary anemia. Among other complications that may be met with at this period are pneumonia, ulceration of the larynx, nephritis, meningitis, cholecystitis, and bed sores.

During the first half of the fastigium the Peyer's patches that have become involved undergo necrosis; and, during the second half, the necrotic areas slough off with formation of local ulcers in the small intestine, the long axis of which is parallel to that of the bowel. Small circular ulcers may also appear owing to sloughing of necrotic solitary lymph follicles.

At the end of the third or fourth week of the disease, in the majority of cases, the temperature begins to fall, usually also in steplike way (*stadium decrementi*). In the temperature chart thrown upon the screen you will note that this is the stage in which our patient now apparently is. It is just about the time when ordinarily the stadium decrementi should be entered upon. The patient has, however, had two or three doses of Dr. Caronia's vaccine and it is possible that the temperature has begun to fall because of this treatment rather than from the natural course of the disease, since I am told that Dr. Caronia's treatment does lead to an earlier defervescence than we usually meet with.

At this stage and during the coming week, the subjective and objective symptoms should also become somewhat less marked. He is entering the stage when the ulcers in his intestine should be becoming cleaner; they may even be beginning perhaps to granulate, though healing will not have occurred until a couple of weeks later.

During the fifth week the temperature often becomes normal and the patient definitely enters upon the *stage of convalescence*. During convalescence, the temperature usually falls not only to normal but below normal and remains subnormal for some six or eight days. The amount of urine increases and its high color disappears. At this time appetite returns and the patient often begins to gain rapidly in weight. In some patients at this stage the skin peels and the hairs fall out.

Unfortunately, in many cases, before the temperature becomes normal there is an exacerbation of all the symptoms and a *recrudescence* of the fever. Even after a normal temperature of several days there may be a *relapse* with a renewal of the former picture though shorter in course. When there is neither recrudescence nor relapse the patient usually has to remain in bed for three or four weeks before he is able to be up and about. Then still another month will elapse before his strength and health will have been sufficiently restored to permit him to resume his work.

I should have mentioned that during the stadium decrementi, instead of a steplike fall of temperature we sometimes observe in the temperature chart a period of so-called "steep curves" (*amphibolous stage*) in which the morning temperature is low and the evening temperature high, much as in sepsis. As a rule, however, the fall of temperature in typhoid fever is by lysis. Occasionally, one does see a critical fall. I am told

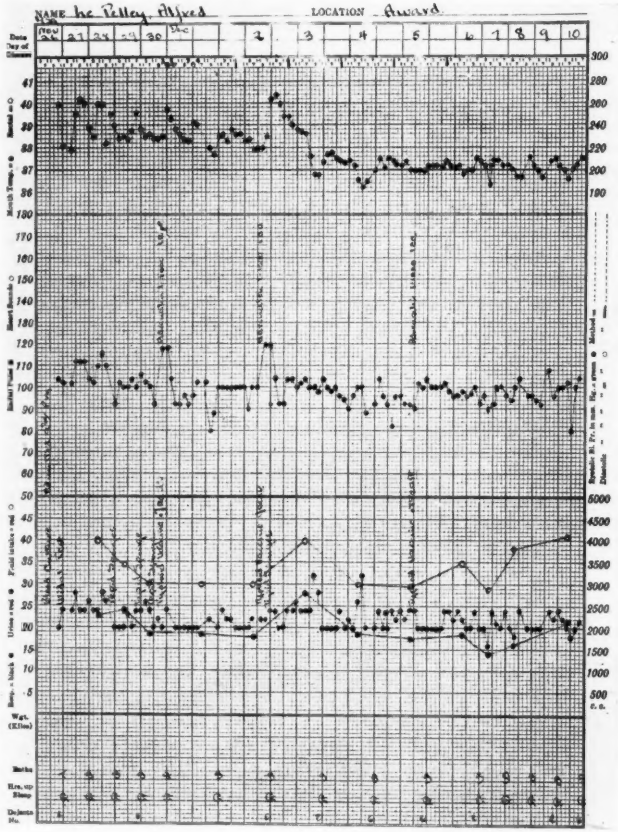

Fig. 1.—Temperature chart of patient with typhoid fever.

that such a critical fall is not infrequently observed after vaccine therapy and after other forms of attempted specific therapy.

If you have attended closely to what I have said you should experience no difficulty in the *diagnosis* of typhoid fever and allied maladies. The clinical appearance of fever of characteristic course, associated with relative bradycardia, with headache, with diffuse bronchitis, with acute splenic tumor, with leukopenia, with a positive diazo-reaction in the urine and with the appearance of typical rose spots upon the

abdomen should make you feel fairly sure that you must be dealing with some member of the *typhoid group of diseases*. It might be typhoid fever proper or one of the paratyphoids, or some other disease that presents a similar picture. In passing, it may be mentioned that herpes labialis is extremely uncommon in typhoid fever and helps us to differentiate it from other maladies (*e. g.*, pneumonia, malaria, influenza, etc.).

But you must depend upon the bacteriological study for the establishment of the precise nature of the infection. *Thus the clinical syndrome alone does not permit us always, as yet, to distinguish typhoid fever from paratyphoid*. You must bring the *direct proof* of the nature of the bacillary infection by blood cultures or by bacteriological examinations of the excreta, or you may attempt to bring *indirect proof* by the demonstration of specific immune substances in the serum (particularly specific agglutinins).

In the *differential diagnosis* there are many diseases that might at first be confused with typhoid fever and they should be definitely ruled out. In the first place other forms of sepsis should be excluded (particularly *streptococcus sepsis*, *staphylococcus septicemia*, and *staphylococcus osteomyelitis*). Then you should rule out also *miliary tuberculosis* which may clinically closely resemble typhoid fever, in the course of the temperature, in the enlargement of the spleen, in the leukopenia, and in the signs of slight meningeal irritation for meningismus is often seen in typhoid. But the blood culture will usually differentiate immediately between the two diseases, since if typhoid fever exists the blood culture, properly made, will be positive for Eberth's bacillus. Should the competently made blood culture be negative when there is high, continued fever that is suggestive of typhoid, typhoid can be ruled out. In addition to this crucial differential test, tubercle bacilli can, in acute miliary tuberculosis, usually be demonstrated in the blood by the antiformin method; moreover, the discovery of a choroidal tubercle on ophthalmoscopical examination, or the finding of multiple minute shadows scattered through the lungs in roentgenograms may give the clue. Occasionally, a *central pneumonia* beginning with a chill may be confounded with typhoid fever. This patient, you will recall, had chills at the onset of his fever. But in pneumonia there is a polymorphonuclear leukocytosis rather than a leukopenia with relative lymphocytosis. Moreover, long before the pneumonic infiltration reaches the surface so as to become demonstrable by percussion, roentgenograms will reveal the existence of the central consolidation. Herpes on the lips would be suggestive of pneumonia rather than of typhoid.

You must not forget, however, that *typhoid fever can coexist with miliary tuberculosis* (though this is rare) and not infrequently *a patient with typhoid fever may develop a pneumonia*.

I cannot take the time to give you all the criteria for differential diagnosis of typhoid fever from *meningitis* (epidemic or tuberculous), from *spotted fever* (typhus exanthematicus), from *relapsing fever*, from *trichiniasis*, from *malaria*, and from *influenza*. After you know the clinical findings, the laboratory findings, and the results of the application of the methods for discovering bacteria or animal parasites in these diseases, you ought to have but little trouble in differentiation.

In recent years in this country there has sometimes been difficulty in distinguishing *undulant fever* from typhoid fever with low temperature curves, though really there should be little difficulty for in the first place in typhoid the blood culture competently made will be positive for the *B. typhosus*, and in the second place the serum of the patient will in cases of undulant fever agglutinate the causative organism. You should know, however, that there appear to be at least three varieties of undulant fever in this country. Dr. Karl Meyer of the Hooper Institute tells me that in the western and southwestern parts of the United States some cases are due to the *Micrococcus melitensis* that causes Mediterranean fevers, some are due to a slightly different coccus that he speaks of as the American strain and some are due to the *Bacillus abortus*. The relations of these undulant fevers to infection in goats, in pigs, and in cattle respectively are now being diligently studied in the Hooper Institute.

PRESENT-DAY CONCEPTIONS OF THE PATHOGENESIS OF TYPHOID FEVER

Though formerly thought to be a primary disease of the intestine itself, students of the pathogenesis of typhoid fever now believe it to be predominantly a disease of the lymphadenoid system of the body with predominant involvement of the abdominal lymphatic system. Typhoid is certainly not a primary disease of the intestinal wall, nor is it a primary disease of the spleen.

It would appear that after typhoid bacilli are taken into the body through contaminated drinking water, milk, butter, cheese, oysters, or vegetables these bacilli enter the tissues and tend to become located and to multiply in the lymph glands, particularly in the lymph glands of the mesentery. The beginning of the incubation period corresponds to the time of entrance of the bacilli into these tissues (rather than merely into the body) and a few days must elapse before the reactions between the multiplying bacilli and the defensive mechanisms of the body give rise to any marked symptoms.

As soon as fever appears and while the fever continues some typhoid bacilli can be demonstrated to be present in the circulating blood, which probably means that there is continuous centripetal transport of bacilli from the primary local foci of multiplication in the lymph glands through the lymph channels and the thoracic duct to the blood and these bacilli entering the blood stream are again continuously being filtered out by various organs (especially the spleen) where they may give rise to local complications. But in addition to the centripetal transport of bacilli from the infected mesenteric lymph glands there may be also centrifugal transport, that is to say, retrograde transport through the lymph channels by means of which Peyer's patches and solitary follicles in the wall of the intestine become invaded, on the one hand, and, on the other hand, the lymphatic channels of the skin of the abdomen are reached, where some of the bacilli multiplying locally and calling forth a hyperemic reaction in their neighborhood give rise to a rose spot (roseola typhosa). You will see in this figure in the article on typhoid fever in Jochmann-Hegler's text-book a good illustration of a section of such a rose spot with great numbers of typhoid bacilli *in situ*. The fact that the rose spots appear upon the skin of the abdomen first and then tend to appear further up or further down upon the trunk and later sometimes upon the extremities, is strongly supportive of the idea of the primary focus of typhoidal infection being in the mesenteric lymph glands, with retrograde transport of bacilli to the lymph channels of the skin.

Many of the complications in distant organs are due to the lodgment in them of typhoid bacilli with local multiplication and local toxic injury. The diffuse bronchitis, on the other hand, may be due to a general intoxication with liberated endotoxins of the bacilli rather than to local deposition of typhoid bacilli in the bronchial walls. A similar toxic

origin of the stuporous and delirious states may be assumed. It must not be forgotten that typhoidal infections may have other infections (due to streptococcus, pneumococcus, bacillus coli, etc.) superimposed upon them.

We now look upon the recrudescences and the relapses that sometimes occur not as being due to reinfection of the intestinal wall from the feces, but rather as a renewal of infection of the intestine from the mesenteric glands by centrifugal transport through the lymph pathways to a new set of Peyer's patches, the mode of recurrence being not wholly dissimilar to that of the relapses of streptococcal infections in the skin in erysipelas.

Nearly all the cases of typhoid fever that come to autopsy appear to have been cases in which the main focus lay in the mesenteric lymph glands. It is quite possible, however, that, in rare instances, other parts of the lymphatic system may serve as the chief focus since occasionally we see typhoid fever without marked involvement of the mesenteric glands and without involvement of the intestinal wall.

REDUCED MORTALITY OF TYPHOID

Whether or not a given typhoid patient will recover depends upon many factors. Thus the severity of the infection in general, the intensity of certain localizations of the bacilli, the kinds of complications that appear, and the degree of their violence—all may be important. Doubtless there are varying grades of virulence in different strains of typhoid bacilli. Moreover, the difference in the resistances of patients must vary enormously. In general, well-marked febrile reactions indicate that a strong fight is going on between the invading organisms and the reacting patients. However, in the milder typhoid cases, the temperature curve may, on the whole, be lower than in severer cases and the fastigium may be markedly shortened. In such mild typhoid cases the invading bacillus may be of a less virulent strain, or the immunity reactions in the patient may occur more promptly, or the patient may have a high natural immunity or an immunity acquired through prophylactic inoculations.

If you will look over the records of the mortality in typhoid fever, you will find considerable variation in different epidemics and in different places the mortality rate varying from, say, 6 to 24 per cent. During the war, when so many were protected by antityphoid inoculations, the mortality varied from 4 to 6 per cent. In persons who had had several antityphoid inoculations the mortality rate varied between $2\frac{1}{2}$ and 5 per cent. You have only to compare the mortality from typhoid fever among our soldiers in the Spanish-American War with that among soldiers in the late Great War to convince yourselves of the efficacy of antityphoid inoculation. It is probable that, at the present time, the mortality rate of typhoid fever, if a large enough number of cases be

considered, will scarcely exceed 5 to 10 per cent. The prognosis seems to be worst in older people and best in children.

TREATMENT OF THIS PATIENT WITH NOTES UPON THE GENERAL MANAGEMENT OF TYPHOID PATIENTS

This patient, though he was ambulatory outside, was placed in bed when he came to the hospital and has been kept there since. He is not permitted to rise for any purpose, even for the passage of urine or stool. He has been sponged regularly. Provision has been made for careful nursing. If I had typhoid fever I should depend more upon a carefully selected nurse than upon all the drugs in the pharmacopoeia.

Formerly we tubbed all typhoid patients, whenever the temperature went above a certain level. Nowadays such systematic tubbing is far less common. If there be hyperpyrexia, we still place the patient in a tub at 32 C. and gradually reduce the temperature to 22 C., keeping the patient in the tub about fifteen minutes. After the tub he is thoroughly rubbed and if he be chilly or blue one gives a little hot black coffee. Care is taken to prevent any exertion on the part of the patient, the tub is brought beside the bed, or the bed beside the tub, and he is lifted in and out of the bath by attendants. One cool tub each evening is important for cleanliness and is also productive of sleep. Of course one would avoid even the disturbance caused by a single tubbing if the patient had recently suffered a hemorrhage or if there were any signs of threatened perforation. Elderly patients are, I believe, better off without tubbing. Moreover, patients who earlier have had heart disease, particularly if there have been any breaks in compensation, should not be tubbed, though cool sponging is permissible.

As to *diet*, this patient has been fed more liberally than was the custom a few years ago. For a long time patients suffering from typhoid fever were kept upon liquid diet (usually milk, alternating with egg albumin) throughout the active stage of the disease. For some years past, however, internists have been feeding their typhoid patients a diet that contained not only a large number of calories, but also a good deal of solid food in addition to liquid nourishment. Experience in America and in Europe indicates that patients thus liberally fed do better and emerge from their illness in a far better state of nutrition than patients kept as formerly upon the partial starvation of an exclusively liquid diet. Thus, in ordinary cases of typhoid fever, one may give as much as 100 Gm. of toasted white bread (or its caloric equivalent in cereals), 100 Gm. of butter, 4 eggs, 100 Gm. of meat (carefully prepared by removal of gristle and by mincing), 50 Gm. of sugar, 50 Gm. of purée of green vegetables, 1 liter or more of milk, and 250 cc. of cream in the twenty-four hours. In addition some orange juice or lemon juice with sugar may be given and will be gratefully taken by the patient. Cracked ice is allowed *ad libitum* for the quenching of thirst. The total fluid in-

take (including water) may, on a régime of this sort, amount to 2000 or 2500 cc. It goes without saying that the diet should be individualized to the special needs of each patient. No physician of experience will agree to hard-and-fast rules of diet in the treatment of all cases of typhoid fever or of any other disease, for that matter.

Very little use of *drugs* is now made in the treatment of typhoid fever. The antipyretics, so much in vogue formerly, and the so-called "intestinal antiseptics," from which so much was expected, have been abandoned. We do not attempt to suppress a febrile reaction in typhoid because we believe it to be useful; if the febrile reaction becomes too violent, it is best controlled, as I have said, by cold baths, wet packs, or sponging, rather than by the administration of antipyretic drugs. We no longer attempt to disinfect the intestine by so-called intestinal antiseptics for two reasons: (1) They do not disinfect the intestine; and (2) the symptoms of typhoid fever are not due to the bacteria in the intestine but depend upon the infection within the lymphatic system and the presence of bacteria in the circulating blood and in the different organs.

We, therefore, make use of drugs in typhoid fever merely when required for the relief of certain symptoms. Thus, we may combat the initial headache by giving codeine in addition to cold applications to the head. If there be diarrhea, a little bismuth subnitrate or calcium carbonate may be useful, or better still, tannalbin or tannigen. When there is constipation, purgatives should not be used; it is best managed by the daily enema, cautiously administered. The old method of treating typhoid with calomel has been abandoned.

Nor is it necessary to give drugs for gaseous distention, for this can be sufficiently controlled by the passage of a rectal tube or by the application of an ice-bag to the abdomen. If hemorrhage from the intestine occurs, it is well to quiet the peristalsis with deodorized tincture of opium or with a little morphine, and the diet should be reduced at once to a very small intake of milk and tea for a day or two.

The *surgical treatment* of typhoid has its place if certain complications occur. Thus, if there should be intestinal perforation, the watch kept upon the patient should have been close enough to have permitted of its recognition and of the performance of laporatomy within one or two hours; many lives have been saved by such close attention on the part of nurses and hospital internes. In the late stages of typhoid, or during convalescence, typhoid osteomyelitis, or local typhoid abscess may require surgical intervention. You will find in the article by Madelung, which I am passing around, a good description of the possibilities of surgical help in various complications of typhoid fever.

Many attempts have been made to apply specific antibacterial and antitoxic treatment as therapeutical measures in typhoid fever, but most of these attempts have thus far been fruitless. You may recall that R. F. Hewlett, among others, made an effort to prepare anti-endotoxic

sera, since the toxin is an endotoxin in typhoid rather than an exotoxin as in diphtheria. Others have tried to prepared bacteriolytic antibodies and to inject them into typhoid patients. An excellent résumé of this subject (up to 1914) will be found in the article by Dr. F. P. Gay. Some have attempted to use detoxified bacilli (old or disintegrated), but without much success (see the 1928 article by Wherry and his associates in the *Journal of Infectious Diseases*). Before the war, during the war, and since, many have made use of vaccine therapy, some using dead bacilli, others living bacilli enfeebled with an immune serum. Still others have used various modified extracts of bacilli.

I have been personally very skeptical with regard to the possible advantages to be gained by such attempts at vaccine therapy. Wonderful as the results have been from protective inoculation, it seemed to me very doubtful if anything could be gained by vaccination methods after the disease has once set in. In Italy, however, the vaccine of Dr. Caronia has been employed and it is said with considerable success. Your Dean, Dr. Langley Porter, tells me that he has seen remarkable effects upon the temperature curves, particularly in children suffering from typhoid fever. Fortunately, Dr. Caronia is at present in San Francisco and is prosecuting researches in the Hooper Laboratory. Dr. Kerr has enlisted his aid in the treatment of this patient, who has begun to receive vaccination by his method as a therapeutical measure. Only two or three doses have, as I understand, as yet been given. Though the temperature has begun to fall the patient is just at the stage of his disease in which the stadium decrementi might naturally be expected to set in. It would have been a fairer test of Dr. Caronia's vaccine if it could have been applied two weeks earlier. Dr. Kerr tells me that Dr. Caronia's vaccine is prepared as follows:

The typhoid bacilli are mixed with immune serum from a patient and this is repeated twice or three times until the organisms have become broken up and the mixture is fairly clear. Then the mixture is centrifugalized and the supernatant fluid, which contains the extractives from the broken-up typhoid bacilli, is put into ampules or other containers to be used as a vaccine in treatment. The sediment contains practically no organisms when the preparation is properly made. Similar methods are employed in preparing other vaccines, such as those from *Micrococcus melitensis* or *Bacillus abortus*. Other organisms of the typhoid-colon group may be handled in the same way.

I have had no personal experience with the use of this vaccine introduced by Dr. Caronia, though yesterday I ran across a report from Italy in which in a series of over 100 cases the mortality rate was said to be about $7\frac{1}{2}$ per cent. In ordinary epidemics the mortality rate today ought to average between 5 and 10 per cent. But even if the vaccination did not lower the mortality rate, we could be grateful if it changed the course of the disease or ameliorated the condition of the patient during

the course. I shall be interested in following the further experiences of the profession with this method of therapeutical vaccination.

PREVENTION OF TYPHOID FEVER

Since all typhoid fever comes from preexisting cases of typhoid in human beings, it is our duty to see to it that this patient is prevented from being a source of infection to others. You have noticed the precautions that are being observed here in the amphitheater. Up in the ward, similar precautions are taken and everything emanating from the patient, especially the urine and the feces, will be carefully disinfected. Moreover, after the patient has recovered we must make sure that he does not remain a bacillus shedder, for many typhoid patients give off bacilli intermittently for some time after they have recovered from their attacks. I myself had typhoid fever at the age of eight and thirty-five years later when Dr. Finney removed four large gallstones from my gallbladder the typhoid bacillus was recovered from the center of one of them in pure culture.

We speak of persons who give off typhoid bacilli in the feces or urine as *typhoid hosts*. A part of these hosts are persons who have had typhoid fever and who have recovered and have become continuous or intermittent shedders, perhaps because of the presence of typhoid bacilli in the gallbladder or in the biliary ducts. But a part of the typhoid hosts are apparently persons who have never had typhoid fever and who may seem to be perfectly healthy. These are the so-called "healthy carriers," and they may be of great danger to single persons, to households, and to communities. One of the gravest menaces to a community is a hotel cook who is a typhoid bacillus carrier.

Endemic typhoid is usually due to bacillus carriers, or to intermittent shedders, who contaminate food and particularly milk, whereas the *large explosive epidemics* over wide areas are nearly always due to an infected water supply. Fortunately, so much interest has been aroused in public health during the last few years that city health boards and state boards of health are ever on the watch for sources of typhoid infection. Only a few years ago Dr. Geiger of this city, by methods worthy of a professional bacterio-detective, discovered the obscure mode of contamination of a water supply that was responsible for an outbreak of typhoid fever in Santa Barbara. The great diminution in the incidence of typhoid in my time has been due to the newer laws and to the hygienic regulations by health boards that have provided for good water supplies and for wholesome milk supplies.

Whenever a case of typhoid fever occurs and is reported to the health authorities, it is important that they should make, immediately, an investigation of those who have been in contact with the patient, for many mild cases will thus be found that would otherwise be entirely overlooked and such mild cases may easily be the means of spreading the

disease more widely. In one small epidemic reported in the literature, only 8 cases had come under the eyes of doctors and been diagnosed as typhoid fever, whereas an investigation of the community by a skilled bacteriologist and epidemiologist indicated the presence of no less than 72 infected persons!

It is not practicable to isolate all typhoid-bacillus carriers, nor is it possible by any method yet known to us to convert every shedder or carrier into a nonshedder or noncarrier, but the health authorities of our cities and towns can see to it that precautions regarding the disinfection of excreta are observed and, still more important, the rule that typhoid hosts shall not be allowed to have anything to do with the preparation of food or with the supply of drinking water should be strictly enforced. Removal of the gallbladder has been attempted as a possible cure of healthy carriers; but aside from the fact that one could scarcely compel all such carriers to submit to cholecystectomy, experience has shown that the removal of the gallbladder does not always accomplish what is hoped for; some carriers have continued to give off bacilli after the operation, probably because of infection of the upper biliary passages.

Much can be done as experience during the war and since has proved to prevent the incidence of typhoid by means of prophylactic inoculations. Very few are susceptible to the disease after such inoculations and those who do contract it exhibit a typhoid fever of mild form and of brief course. Three successive doses of vaccine are given by subcutaneous injection at intervals of one week or ten days, after which the person will be well protected for at least one year or two and will show a positive Widal reaction in his serum for the ensuing nine months. When typhoid is prevalent, or when one is undertaking a journey into foreign countries where typhoid may be prevalent, prophylactic inoculation would seem to be highly desirable in persons who have not already suffered from an attack.

You will see from what I have said that our conceptions of the nature and pathogenesis of typhoid fever, of the mode of its spread, of methods of recognizing it, and of methods of treating it, and of preventing it, have undergone marked changes during the past quarter of a century. It would seem quite possible that typhoid may wholly die out, in which event the medical students will know of it only through historical studies. Even today, as I have said, it is very uncommon contrasted with its frequency twenty-five years ago. I am very glad indeed to have had the opportunity of bringing this case before a class of medical students who may have little opportunity of observing it.

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A LUETIC PATIENT WITH SEVERE MEGALOCYTIC ANEMIA OF THE ADDISON-BIERMER TYPE AND PERSISTENT VOMITING RESCUED BY LIVER EXTRACT ADMINISTERED THROUGH THE DUODENAL TUBE[1]

THIS patient was so ill last July that her life was despaired of. She suffered from an anemia so severe that her red cell count had fallen to 900,000. Nausea and vomiting were so pronounced that food and medicines administered by mouth were not retained. Fortunately, by the introduction of a suitable remedy through a duodenal tube, her life has been spared, and she has since made rapid progress toward recovery.

The case illustrates so well some of the principal features of a form of anemia, with which every medical practitioner needs to be well acquainted, that Professor Kerr has chosen it for me to present to you at the clinic this morning. After hearing the data as collected in the hospital record, a summary of which has been prepared by Dr. R. B. Smalley, we may discuss the diagnosis and treatment and comment upon the etiology of the malady and its pathogenesis.

SUMMARY OF CASE HISTORY

The patient, B. H., a white woman, age fifty years, housewife, was first admitted to the University of California Hospital on July 23, 1929.

Complaints.—Weakness, shortness of breath, vomiting, jaundice, and rapid loss of weight during the preceding ten months.

Family History.—This was unimportant, as far as elicited, except that the patient's father died at the age of sixty-eight of cirrhosis of the liver.

Previous History of Patient.—She has always lived in California and is by occupation a housewife and cook. Menstruation began at the age of ten (premature puberty). She has been married twice, first at the age of fifteen, living with her husband until she was twenty-one, during which time there were two induced abortions; she married a second time at the age of forty-nine.

During adolescence, she had frequent attacks of tonsillitis and the tonsils were excised when she was eighteen. Before the onset of her present illness she had long been obese, averaging 230 pounds in weight, and she states that, owing to her excessive weight, she easily got out of breath on physical exertion. She suffered from occasional "bilious attacks," which she ascribed to overeating, but otherwise she was regarded as fairly healthy until the onset of her present illness in October, 1928.

History of Present Illness.—Nine months before entry to the hospital she awoke one morning, feeling nauseated and weak. She vomited several times and, during the following day, became definitely jaundiced. She soon began to have a roaring sensation in the head and ringing in her ears. She noticed that she was becoming short of breath and progressively weaker. Vomiting recurred at times, usually several hours after eating, but she does not recall the appearance of the vomited materials. Menstruation ceased at about the time of onset of the present illness.

[1] Clinic at the University of California Medical School, Monday, December 2, 1929.

During her illness she had lost, up to the date of admission, some 70 pounds in weight. She had no pain, no headache, no paresthesia and no diarrhea. For a few weeks before entry she complained of feeling cold much of the time.

Physical Examination (July, 1929).—Though the patient had lost 70 pounds, she still weighed 160. She looked very ill, was dyspneic and weak and was slightly, but definitely, jaundiced. There was involuntary twitching of the hands and feet. The pulse rate was accelerated but the pulse was regular, with visible peripheral pulsations. The blood pressure was 110 systolic, 50 diastolic. The lungs were negative, except for dyspnea. The heart's apex was palpable medial from the midclavicular line in the fifth interspace; a loud blowing systolic murmur was audible at the apex and over the body of the heart. No diastolic murmur could be heard. No marked accentuation of second sounds was made out.

The abdominal wall was relaxed. There was some tenderness on palpation below the umbilicus, 4 cm. to the right of the midline. No evidence of fluid in the abdominal cavity. Liver dulness extended three finger's breadth below the costal margin. The tip of the spleen was palpable in the left hypochondrium; it was firm but not tender. Abdominal reflexes could not be elicited. Deep reflexes in the extremities were active and equal. The Babinski test was negative on both sides.

Laboratory Reports.—*Blood.*—Red blood cells, 900,000; hemoglobin, 21 per cent; color index 1.16; white blood cells, 3200. Differential count in stained smears showed polymorphonuclear neutrophil leukocytes, 70 per cent; small mononuclears, 30 per cent. There was marked anisocytosis and poikilocytosis. Many large oval megalocytes were present. The platelets were decreased. Reticulated count 0.6 per cent. Icteric index 20. Wassermann in blood serum 4 plus on three different tests.

Cerebrospinal Fluid.—Negative.

Urine.—Cloudy, yellow, specific gravity 1.012, acid reaction, with a trace of albumin. Urobilin test positive; no sugar. Epithelial cells and a few white corpuscles in sediment, but no red cells and no casts.

Stool.—Negative.

Diagnosis.—1. *Pernicious anemia* (of severe grade, without glossitis and without neurological symptoms and signs except twitching of hands and feet and loss of abdominal reflexes on admission last July—but she has developed paresthesias since).

2. *Lues* (Wassermann positive in blood; negative in cerebrospinal fluid).

3. History of *obesity* (weight was 230 with loss of 70 pounds).

Course in the Hospital.—When the patient entered the hospital she seemed so ill as to be almost "at the point of death." Intravenous glucose was administered. An attempt was made to give liver extract by mouth, but she vomited it. One vial was then given through the duodenal tube thrice daily for a time. Within a few days large numbers of reticulocytes appeared in the blood and soon the red cell count began to increase and the hemoglobin percentage rose steadily. Mercurial inunctions were begun, and as soon as the stomach would bear it, the liver extract was administered by mouth and she was given a diet rich in calories. Dilute hydrochloric acid was given thrice daily as well as some sodium iodide.

She remained in the hospital for four weeks, at the end of which time she had vastly improved and felt very well; the red count had risen to 3,000,000 and the hemoglobin to 60 per cent.

On discharge (August 20, 1929), she was instructed to continue to take one vial of liver extract thrice daily, and a teaspoonful of dilute hydrochloric acid with each of the three meals. She was to report to Division L regularly for antiluetic treatment.

DIAGNOSIS OF THE ADDISON-BIERMER TYPE OF ANEMIA

The diagnosis of the Addison-Biermer type of anemia can now be made with great certainty in the vast majority of cases in which the disease exists. It is only in rare instances that there should be any doubt

about the diagnosis, provided the patient can be studied in a competent manner. We can make the diagnosis even in cases in which the hemoglobin percentage is as high as 90 or even 100 per cent, if the proper tests be skilfully applied and if the results of the test be judged in the light of the knowledge that has in our time been gained.

The *clinical history* and the *physical examination* often give us important clues. Among the early symptoms and signs that may excite suspicion, I would emphasize soreness of the tongue, lassitude and fatiguability with pallor, and especially with a straw-colored tint to the skin; digestive disturbances, especially unmotivated diarrhea; and paresthesias of the hands or feet. Moreover, if, on *routine laboratory examination* of any patient, we should find a high color index, a urobilinuria, or an achylia gastrica, the idea of the possibility of the existence of Biermer's anemia should at once leap into consciousness, and the study of the patient should be extended until the presence or absence of the disease is definitely determined.

A *careful study of the blood* will definitely establish the diagnosis of this disease (when it exists) in more than 90 per cent of the cases; indeed, unless the diagnostic criteria of the blood are decisive, one would hesitate to make the diagnosis of Biermer's anemia, no matter how suggestive the other data accumulated may seem. As long as there is doubt about the blood picture itself, the diagnosis of Biermer's anemia should be made merely tentatively, rather than positively; the mind should remain open until the studies of the blood yield findings that either verify or refute the diagnosis.

In the patient before you today the blood picture (Fig. 2), together with the clinical picture as a whole, leaves no room for doubt, since we here have to deal with a fairly typical and outspoken example of Biermer's anemia. The case is an excellent one for the class of students to see, for once you have become acquainted with the main features of such a typical case, you should not only easily recognize other typical cases, but should also have laid the foundations for the appraisement of cases that are less well characterized.

In the blood picture of our patient today, the tremendous reduction in the red cell count to 900,000 (*oligo-erythrocythemia*), the low hemoglobin percentage of 21 (*total hypochromemia*), with the fairly high color index of 1.16, indicating increase in the average corpuscular holding in hemoglobin, the marked inequality in the size of the red cells (*anisocytosis*) and the distorted shape of these cells, many of them being "tailed" (*poikilocytosis*), the presence of large numbers of oval red cells of greatly increased diameter (*megalocytosis*), the dark golden-yellow blood serum as shown by the inspection of the serum and by determination of the icteric index of 20 (*bilirubinemia*), the decreased number of platelets (*hypothrombocythemia*), and the marked reduction in the number of white blood corpuscles to 3200 (*leukopenia*) are features that are so character-

istic of Biermer's anemia (formerly referred to as "pernicious" anemia) that there can be no doubt that you had to deal with a pronounced example of that malady. In one point only does the blood picture as reported deviate from the typical; the differential count of the white corpuscles, despite the well-marked leukopenia, showed no relative diminution of the polymorphonuclear neutrophils and no relative increase in the small mononuclear elements, whereas ordinarily in Biermer's anemia the leukopenia is associated with an absolute and relative *neu o-penia* and a relative *lymphocytosis*. Possibly, differential counts

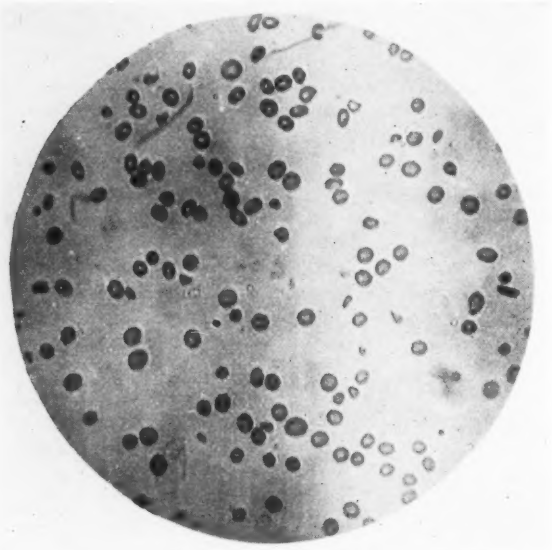

Fig. 2.—Blood smear of patient with pernicious anemia showing megalocytosis, anisocytosis, and poikilocytosis.

made at different times might have revealed such changes in this patient.

Such a blood picture as this patient exhibited on admission last July represents a full-blown Biermer syndrome of severe grade, though not the severest grade that has ever been met with, since in extreme instances the red cell count has been found as low as 138,000 or even 110,000, the hemoglobin percentage as low as 20, 10 or even 7 per cent, the color index as high as 1.7 or greater, and the leukopenia as marked as 2000 or less with reduction of the neutrophils to 500 or even 100, and of the monocytes and eosinophils to 1.

In the blood picture most frequently observed in Biermer's anemia, the white count varies between 2000 and 4000, the monocytes are markedly reduced in numbers, the eosinophils do not exceed 1 or 2 per cent, and the lymphocytes make up 50 per cent or more of the total white count. There is usually some polychromasia of the red cells, though nucleated red cells are usually but few in number until improvement sets in; still occasional normoblasts and megaloblasts may be seen in thick blood specimens prepared by the method of Ross. In the *remissions* that we often saw, even before the introduction of the liver treatment, the red count often rose to 2,000,000 or 3,000,000, the hemoglobin percentage rose to 60 or even 90 per cent, the microcytosis and poikilocytosis temporarily disappeared (though the megalocytosis continued), the white count increased to 6000 or 10,000, and the neutrophil cells increased in numbers, as did the eosinophils, the monocytes, and the blood platelets. During such remissions, we occasionally met with so-called "blood crises," in which many nucleated red cells appeared in the blood, polychromasic red cells, as well as red cells with basophilic stippling increased in number, the absolute neutrophil count became markedly increased with corresponding decrease in the relative lymphocytic preponderance, large clumps of platelets were observable, and a few myelocytes appeared—all these signs pointing to temporary hyperactivity of both the erythropoietic and the leukopoietic functions of the bone marrow, this hyperactivity replacing for a time the relative inactivity or torpor of the bone-marrow functions in pernicious anemia.

In the *differential diagnosis* of Biermer's anemia, it should not be forgotten that there are certain other anemias with megalocytosis and with high color index that must be excluded before we can conclude that we have to deal with a true Biermer type. Among these may be mentioned: (1) The anemias that accompany *malignant neoplasms involving the bone marrow* (history; discovery of neoplasm; roentgenograms of bones; myelocytosis; less leukopenia, etc.); (2) the anemias that accompany *leukemic* and *aleukemic myeloses* (higher red count; deviating white cell picture); (3) *acquired hemolytic anemia* (increased fragility of red cells; leukocytosis; increase in neutrophils; many monocytes; abundant platelets); and (4) certain severe anemias of childhood, especially the so-called *anemia pseudoleukemica infantum* of v. Jaksch and Hayem (marked leukocytosis; many nucleated red cells; marked splenomegaly and hepatomegaly; age).

On the other hand, we meet sometimes with cases of *atypical Biermer's anemia* in which there is marked deviation from the characteristic blood picture of this malady. Thus, I have already referred to the altered blood-picture concomitant with the so-called *blood crises* that may occur in the course of the disease. Again, if the Biermer patient should have *marked hemorrhages*, the color index may fall below 1 and the individual red cells may look pale, though the megalocytosis may still be easily

demonstrable by appropriate methods. Furthermore, the occurrence of outspoken *septic processes* in the course of Biermer's anemia may cause marked leukocytosis, myelocytosis, and erythroblastosis that may temporarily be very puzzling. And, finally, should a Biermer patient develop a *carcinoma of the stomach*, the whole blood picture may undergo such alteration that had not one known earlier the existence of the Biermer anemia, he might not be able to recognize it in its changed relationships.

The *recognition of the existence of an outspoken megalocytosis and of its grade* is of such great importance for the diagnosis of the anemia under consideration that an acquaintance with the methods that may be used to determine it would seem to be in place. Of course, in a well-marked megalocytosis, the mere inspection of the fresh blood slide will reveal it immediately to the trained eye and the high color index alone is very suggestive of it.

Alder's method of determining the average volume of the individual red cells is very useful. The relative volume of the corpuscles to the plasma is determined first by centrifugalization in the hematocrit or by the refractometric method, and then the average volume of the red cells can be calculated if we know the red cell count. The relatively few white cells and platelets do not materially influence the result. Thus, in normal blood, we have 5,000,000 red cells per c.mm. and the volume of red cells measures 0.44 mm^3. The average volume of 1 red cell = 0.44 mm^3 : 5,000,000 = 88 μ^3; an easy method of calculation is to divide the volume of the centrifugate per cubic millimeter multiplied by 1000 by the number in millions of red cells per cubic millimeter (thus 440 : 5 = 88 μ^3). Experience has shown that in carcinoma the average volume of the red cells is approximately normal and that in tuberculosis it is reduced (microcytosis). In secondary anemias it is reduced (in extreme instances to 60 μ^3); in hemolytic anemias it may be slightly increased (say to 90 or 95 μ^3); whereas in Biermer's anemia it is markedly increased (often to 120 or 165 μ^3).

Another way of determining the degree of megalocytosis is by charting the diameters of 500 red cells by the Price-Jones method. This is a time-robbing method requiring several hours of work by a skilled observer, but its results are corroborative of the other methods.

Perhaps the best way of determining the degree of megalocytosis is by means of the diffraction method of A. Pijper or the modification of this devised by F. C. Eve. It has long been known to physicists that if a beam of light be passed through a thin layer of minute particles, haloes are produced, due to the interference of the light waves by the particles; the finer the particles, the bigger the haloes. Pijper places a dry unfixed blood smear in the path of a strong beam of light derived from a pointolite lamp (through a suitable condenser lens and an iris diaphragm); at the back of the blood film is placed a simple lens with a focal distance of 20 to 60 cm., and this focusses concentric spectra upon a sheet of

white paper. By a simple formula it is easy to determine the average diameter of the red cells.

This diffraction method has been made still simpler by Eve, who found that he could use a reflex camera (1927 Thornton-Pickard, with F. A. 4.5) for the purpose. All that is necessary to do is hold a blood smear in front of the lens when the camera is fully extended and is focussing on the filament of a focus lamp (Osram, 100 watt). One looks into the hood and sees two concentric haloes colored brighter than a rainbow. By a millimeter scale on celluloid, one measures the outer diameter of the inner halo; normal blood yields a measurement of 32–33 mm. If the halo measures below 30 mm. one may be sure of a degree of megalocytosis such as is met with in pernicious anemia or in some cases of subacute combined degeneration of the spinal cord (funicular myelopathy). In severe megalocytosis with marked poikilocytosis, the colors overlap so

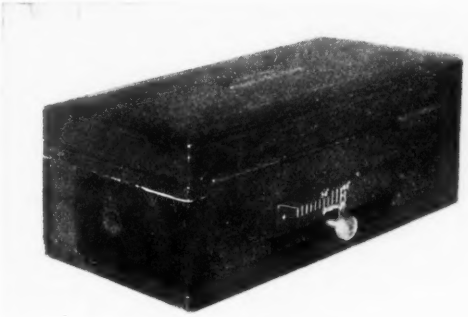

Fig. 3.—Eve's halometer.

that the haloes appear more or less uncolored and "mossy-edged"; here one measures the outer diameter of the small uncolored hazy halo. Eve reports that before treatment this small colorless mossy halo may measure only 25 mm. but after a few weeks of liver treatment one will see a beautifully colored sharp halo of 29 mm. diameter. A few weeks more of treatment by liver and the halo will grow to normal size (32 mm.). He gives specific directions for making blood films only one cell in thickness. This method, which sounded simple and practical, should, I thought, be given a trial. But in a recent number of the *British Medical Journal* a still simpler apparatus has been devised and is known as Eve's "halometer." We are fortunate to be able to show you the apparatus (loaned to us by Dr. Cheney) today and to apply it to the smear from this patient. You will observe how simply it works and that within a couple of moments you can read on the scale the average size of the red cells (Fig. 3).

THE MODERN TREATMENT OF BIERMER'S ANEMIA

Since the fundamental researches of Whipple, Robscheit-Robbins, and their co workers (1920–1926) upon the effects of certain foodstuffs, especially of liver, upon the acceleration of blood regeneration in the experimental secondary anemias of animals, researches that were inaugurated here in San Francisco in the Hooper Foundation for Medical Research, we have entered upon a wholly new era in the therapy of the anemias. Stimulated by the researches mentioned, Minot and Murphy began the treatment of cases of Biermer's anemia with liver diet and in the autumn of 1926 published a series of 45 cases in which they had observed strikingly favorable results. In July, 1927 they reported on some 125 cases of this form of anemia; they fed their patients daily about 200 Gm. of cooked or raw calves' liver and beef liver, along with much fruit, vegetables, and meat, limiting the intake of fats and sweets. The calories of the diet were brought up to 2000 or 3000 by the addition of eggs, milk, bread, potatoes, and cereals (roughly 340 Gm. carbohydrate, 135 Gm. protein, and not more than 70 Gm. fat).

The results obtained by this diet were so remarkable that the news rapidly spread over the whole world and since 1927 enough reports have come in from every quarter of the globe to make it certain that liver treatment of Biermer's anemia must be counted as one of the greatest therapeutical triumphs of modern times.

Very quickly after the liver diet is begun, numerous young erythrocytes easily demonstrable by vital staining—the so-called "reticulocytes"—appear in increasing numbers in the circulating blood. The following of the reticulocyte count is an excellent gauge of the effectiveness of the therapy. Patients with from 0.1 to 1.5 per cent of reticulocytes in the blood before liver treatment is begun may after two or three days of liver feeding show from 3 to 6 per cent and later on 10 or 15 per cent or more; in some cases after a week or two as high as 50 per cent. If the reticulocytes do not rise, it is because insufficient liver is given, because septic or other complications exist, because the bone marrow cannot respond, or because a mistake in diagnosis has been made. Besides the appearance of these reticulated young red cells, there is a rapid diminution of the number of poikilocytes and megalocytes, a steady increase in the hemoglobin percentage with decrease of the color index, an increase in the number of white corpuscles, especially of the neutrophils, the eosinophils, and the monocytes, an increase also in the number of blood platelets, and a fall of the icteric index. After the blood has approached a normal state again, the reticulocytes decrease to a small percentage, and smaller amounts of liver will maintain the normal blood picture.

The amounts of liver necessary are so large that there is often difficulty in persuading patients to eat enough, despite the ingenuity of dietitians in preparing it in palatable forms. The isolation of effective

liver extracts by Cohn and Minot, by West and by others, and their substitution for the feeding of liver were, therefore, most heartily welcomed; and experience has already shown that if sufficiently large doses of these extracts are administered (say an amount of extract equivalent to 600 Gm. of liver daily until the red count returns to normal, and afterward an amount equivalent to 200 Gm. of liver daily to maintain the count), the patients respond as they do to the feeding of the crude liver. Reports to this effect are coming in from many medical centers. You have found the liver extract effective in this hospital and last May, at the California Medical Association, Wyckoff and Bloomfield, of the Stanford University Medical School, reported in detail some 5 cases of pernicious anemia in which the response to liver extract was similar to that occurring after feeding with whole liver.

The patient before you is proof of the advantage of having liver extract available, for owing to vomiting she could not at the beginning of the treatment retain liver or other foods; she even vomited the liver extract given by mouth; fortunately, through the passage of a duodenal tube, liver extract could be introduced directly into the intestine and her life was saved.

It is probably wise to give some whole liver as food in addition to the use of liver extract. I think it is also important to give a full teaspoonful of dilute hydrochloric acid with each meal in orange juice or carbonated water (method of A. F. Hurst). Sunlight or systematic exposure to ultraviolet light is an excellent adjuvant to the liver therapy. It will seldom, if ever, be necessary from now on to make use of blood transfusions in the treatment of Biermer's anemia.

Unfortunately, the achylia gastrica and any spinal cord changes that may have developed precedent to the liver therapy do not appear to have been much benefited by treatment with liver diet or liver extract. It looks, though, as if the funicular myelopathy may, sometimes, be stopped in its progress; if ataxia exists it can be largely overcome by systematic re-education of movements as in locomotor ataxia due to syphilis. Recently I have seen marked improvement in the spinal cord symptoms after increasing the dosage of Lilly extract of liver to ten vials per day.

BRIEF COMMENT UPON THE ETIOLOGY AND PATHOGENESIS OF BIERMER'S ANEMIA

The clinical picture of Biermer's anemia may occur as a result of infestation with the tapeworm, *Bothriocephalus latus*, of pregnancy-intoxication, or of luetic infection, but in the majority of cases no obvious parasitism or intoxication has been found (cryptogenetic cases). Efforts to explain these cryptogenetic cases by the assumption of focal infections, or of gastro-intestinal intoxication due to achylia gastrica as etiologic factors have been unsatisfactory. One dare not maintain that any etiological factor is responsible for a Biermer's anemia unless

on removal of the assumed factor the patient remains free from recurrences and is permanently cured (as, for example, after expulsion of a tapeworm, the termination of pregnancy, or the cure of syphilis).

Because of the toxic nature of the cases of known etiology, it has been assumed that in all cases of Biermer's anemia the cause must be some erythrocytotoxic agent. Support to the view of a toxic origin was given by Macht who found the serum of Biermer cases definitely phytotoxic by his growing-bean test.

Those who adhere to an erythrocytotoxic origin looked upon the bone marrow changes as compensatory attempts to supply new blood cells. Some believed that the spinal cord changes must be due to the same "toxin"; others assumed the existence of two toxins—one hemotoxic, the other neurotoxic.

A constitutional factor has been strongly urged by Martius and others, who looked upon the achylia gastrica as a necessary forerunner of the anemia and a part of the constitutional inferiority. These authors also assumed the existence of a constitutional inferiority of the bone marrow. The multiple occurrence of Biermer's anemia in certain families and the fact that certain patients who recovered from bothriocephalus anemia after expulsion of the tapeworm developed, years later, a cryptogenetic pernicious anemia lent support also to the view that a constitutional factor may be of importance.

Some authors then adopted the view that though a constitutional factor may be present, a variety of intoxications may be responsible as "releasing factors."

One thing was striking, namely, the monotony of the blood picture despite the multiplicity of assumed etiologic toxic agents. That the red cells of the Biermer patient are more vulnerable than foreign blood cells introduced by blood transfusions has recently been demonstrated by P. Morawitz who, in some patients, found that, after numerous transfusions, the red cells in the circulating blood were nearly all donor's cells, the receptor's cells having been more rapidly disintegrated.

Since the advent of liver therapy wholly new theories of pathogenesis have been promulgated. Some favor the view that Biermer's anemia must be looked upon as a disease due to dietetic deficiency, akin to the avitaminoses (like pellagra, scurvy, beriberi, and rickets). A study of pre-anemic diets by Cornell favored this view, as did the success of the liver-diet treatment. Others have advanced the hypothesis that the normal functioning of the bone marrow is dependent upon an internal secretion of the liver and that in Biermer's anemia this specific incretum is lacking; liver therapy is for them, therefore, an endocrine therapy, in other words, a substitution therapy analogous to the treatment of myxedema by thyroid extract or of diabetes mellitus by insulin. Even with this view, the origin of the hepatic endocrine insufficiency remained obscure, though some would explain it by toxic or infectious injuries to

the liver. It must not be forgotten either that organs other than the liver contain the same or a similar effective substance. Thus kidney and muscle contain it, as does the wall of the stomach and intestine. Dr. Immerman has called my attention to the article by Sturgis and his associates upon the effectiveness of hog's stomach. Recent studies suggest that fetal livers may be even more effective than ordinary liver.

In my opinion, we are only beginning to grasp the links in the pathogenetic chain of Biermer's anemia. Before the pathogenesis is fully understood, we shall have to become better informed regarding the origin of the glossitis, the achylia, and the funicular myelopathies, as well as regarding the disturbances of hepatic function.

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MODERATE ANEMIA CONFORMING TO THE BIERMER TYPE (EXCEPT FOR AN ACCOMPANYING LEUKOCYTOSIS) IN ASSOCIATION WITH GLOSSITIS, ACHLORHYDRIA GASTRICA, AND PARESTHESIAS IN THE EXTREMITIES; DIFFERENTIATION OF PERNICIOUS ANEMIA FROM OTHER ANEMIAS THAT MAY SIMULATE IT[1]

In the clinic preceding this I showed you a typical case of pernicious anemia of the Addison-Biermer type; the patient had been rescued from impending death through the intraduodenal administration of liver extract. The clinical findings, together with the blood picture, were, in that case, so characteristic that no doubt could remain in the mind as to the validity of the diagnostic conclusion at which we arrived. Now, I desire to present to you another case of anemia that, in many respects, conforms to the Biermer type, but, as you will learn during the course of the hour, is peculiar in that the blood picture shows a leukocytosis instead of a leukopenia and there is a relative increase in the polymorphonuclear count rather than a relative lymphocytosis. Such findings as the latter should put us on our guard and compel us to be cautious and to hold our minds open temporarily before deciding upon the final diagnosis. The Addison-Biermer type of anemia can be simulated by a number of other conditions and one must always be careful to exclude as many of these other conditions as possible, in instances in which the blood picture is atypical in any way.

CASE HISTORY

The patient, H. E. H., a retired clerical worker, age sixty-seven years, is a private patient of Dr. F. H. Kruse. He has kindly consented to come here today in order that we may discuss his case before the class. The history I shall give you has been summarized from Dr. Kruse's clinical records of the case.

When the patient came for diagnosis and treatment on October 21, 1929 he mentioned a variety of complaints: (1) Dizziness for four years with occasional attacks of nausea and vomiting followed by "fainting spells"; (2) impairment of taste for four years with burning of the tongue especially when hot foods were taken or when toothpaste was used; (3) sensation of "pins and needles" in the hands and feet for two months; (4) poor appetite with gradual loss of weight for three years; and (5) shortness of breath recently on exertion.

Past History.—The patient's habits have been good; though he chews tobacco, he does not smoke, and he does not take any alcohol. He has been singularly free from infectious disease throughout his life. He has never been operated upon and has never suffered any traumata. He has occasional colds, but has never had tonsillitis. Since his present illness he has been short of breath on exertion, but he has been able to walk as much as ten miles per day in spite of it. His appetite has been poor. The bowels have been regular. He has had occasional heart burn, approximately once a month. He has worn glasses because of failing vision and has been somewhat

[1] Amphitheater Clinic at the University of California Medical School, Monday, December 2, 1929.

deaf in his right ear for a long time. During the past three years, he has lost weight gradually.

Family History.—Father died at forty-two of pneumonia; mother died suddenly at sixty-four, cause unknown; three brothers and one sister living and well. No history of anemia, epilepsy, tuberculosis or carcinoma in the family. The patient's wife died twelve years ago; two children, a son and a daughter, are living and well.

Present Illness.—Up to four years ago, the patient regarded himself as very well, but at that time he began to have dizziness with nausea, weakness, and fainting spells, and the burning of the tongue and impairment of taste mentioned among his complaints also appeared at that time. It was only recently that he began to have "pin and needle feelings" in his hands and feet. His friends have noticed that he has been growing pale and that his lips were somewhat bluish at times. Most of his teeth have been removed. He stated that his spine had grown a little stiff.

Physical Examination.—He is 28 pounds under calculated ideal weight and looks markedly undernourished. The lips and mucous membranes are pale. The sclerae are of a bluish tinge. There is no jaundice. The mouth shows atrophic glossitis and many teeth have been extracted. The tonsils are small and do not seem to be infected. There is no struma and no enlargement of lymph glands anywhere. He has had slight fever at times, but the temperature is now normal. Aside from some limitation of the movements of the spine, examination of the joints is negative.

The chest is emphysematous in type and some crackles are audible over both lower lobes, evidently due to chronic bronchitis. The pulse rate is slightly accelerated and there has been some irregularity of the extrasystolic type. The heart is moderately enlarged to the left. A soft systolic blow has been audible at the apex and the aortic second sound is a little accentuated. The blood pressure is 144 systolic, 70 diastolic. The peripheral arteries are somewhat thickened.

Abdominal examination has been negative. There is no enlargement of the spleen or of the liver. Rectal examination is negative except that the prostate is slightly enlarged and firm, but it is smooth.

Despite the patient's paresthesias, no objective disturbance of sensibility has been made out, except slight diminution of the vibration sense. The deep reflexes are somewhat hyperactive; the pupils react normally. There has been no tremor.

Laboratory Examinations.—*Blood.*—Red cells 2,710,000 to 3,150,000; hemoglobin 60 to 74 per cent; color index about 1.2; white cell count 11,900 to 13,600. Differential count: Polymorphonuclear neutrophils vary between 75 and 86 per cent; small mononuclears between 16 and 23 per cent; the large mononuclears and transitionals have been as high as 10 to 15 per cent. The smears show some anisocytosis with some large oval megalocytes and there is some poikilocytosis, and a number of polychromasic cells. The reticulocyte count has varied between 0.8 and 1.7 per cent. The Wassermann reaction has been negative.

Stomach Contents.—Free hydrochloric acid, 0. Total acidity 14 to 25 acidity per cent; no Oppler-Boas bacilli present; no occult blood.

Stool.—Negative for occult blood and for parasites.

Liver Function Tests.—Marked hypoglycemic shock with the glucose-insulin test indicates some damage to the blood sugar regulating function of the liver; rose bengal test has not yet been applied.

Urine.—Negative except for urobilinuria.

Basal Metabolic Rate.—Normal.

***x*-Ray Examinations.**—In roentgenograms of the chest, the lungs have been negative, the shadows due to the heart and aorta look normal. Gastro-intestinal series made by Dr. Ruggles, negative. Gallbladder visualization test, normal. Roentgenograms of the teeth are negative.

Electrocardiogram (made on October 29th) showed a heart rate of 82; there was normal rhythm when the record was made. P_1 was notched, P_2 was diphasic; there was inequality of the atrial contractions and slight right axis deviation (Dr. Sampson).

Discussion of the Clinical Findings.—From the diagnostic standpoint the interest in this case centers in the decision to be made regarding the precise nature of the anemia. In favor of the idea of a pernicious anemia of the Addison-Biermer type is the history of marked weakness, dizziness, and dyspnea in association with glossitis, achlorhydria gastrica, paresthesias in the extremities, pyrexia, and urobilinuria. The fact that the color index is high also points to pernicious anemia.

But against typical pernicious anemia are the following facts: (1) There has never been a leukopenia, the white cell count being on different occasions, 8300, 9100, 11,900, 12,000, and 13,600; (2) the differential counts have shown a relative increase of the polymorphonuclear elements—75, 79, 80, and 86 per cent on different occasions.

In one count made by Dr. Rickard on November 4, 1929, the differential count was much more like what one sees ordinarily in pernicious anemia. The white count at that time was 8300 and the polymorphonuclear percentage was only 48.5, whereas the percentage of small mononuclears was 49, the blood platelets were 270,000, the stained smears at that time showed both anisocytosis and poikilocytosis. Two counts made still later, however, showed a larger number of white corpuscles and a higher percentage of polymorphonuclear neutrophils (70.6 and 79.4 per cent). At the present time there are 11,200 white cells, 80 per cent of which are polymorphonuclear neutrophils.

From the data thus far accumulated we are justified in making the following diagnoses: 1. Moderate anemia (red cells 2,680,000 to 3,150,000, with aniso- and poikilo-cytosis, but without outspoken megalocytosis, the hemoglobin varying from 60 to 79 per cent, and the color index varying between 1 and 1.2, in association, usually, with leukocytosis of from 8300 to 13,600, and with a relative polymorphonuclear increase in the differential counts; in only one count was there a decrease of the polymorphonuclears with relative lymphocytic increase. The anemia, however, has been associated with absence of free hydrochloric acid in the stomach juice, with urobilinuria, with recurrent febrile reactions, with atrophic glossitis, and with paresthesias.

2. Arteriosclerosis (with thickened peripheral arteries, slight increase of blood pressure, and slight albuminuria).

3. Cardiopathy (with occasional tachycardia and arrythmia due to premature beats, soft systolic murmur at the apex, transverse position of the heart, and slight changes in the electrocardiogram).

4. Ménière syndrome (of four years' duration), with dizziness, with a history of deafness in the right ear, with attacks of weakness and, sometimes, with syncopal attacks.

5. Slight emphysema with chronic bronchitis.

6. Refraction error (corrected by lenses).

7. Undernutrition (28 pounds).

I cannot help but feel that, in this patient, we must be dealing with an atypical example of the Addison-Biermer type of anemia, or what is ordinarily called "pernicious anemia," though I think that there must be some complication to account for the leukocytosis and the relative increase of the polymorphonuclear neutrophilic elements. Another point that arouses the suspicion that we may be in error in regarding the case as one of pernicious anemia is the absence of outspoken megalocytosis. I think we ought in this case, to measure the average diameter of the red blood corpuscles by means of Eve's halometer and I find that Dr. Cheney's instrument is here today. We can, therefore, make measurements at once, making use of the blood slide that is ready. You will see, on looking through the halometer, that the two spectra come together at a point that corresponds to the upper limit of normal for the size of the individual red cells. Indeed, it just falls within the limit given by Eve for pernicious anemia. There is, therefore, a megalocytosis of moderate degree in this patient, though it is not nearly of so high a grade as was that in the woman with typical pernicious anemia whom I showed to you in a former clinic.

Of the atypical pernicious anemias may be mentioned (1) those that are complicated with septic processes; (2) those in which blood crises occur; (3) those in which there has been marked hemorrhage with a secondary anemia superimposed upon the primary anemia, and (4) those like our patient of today with only slight megalocytosis, and with polymorphonuclear leukocytosis.

We have sought for possible foci of infection in this man, but thus far have not been able to find one that could account for the polymorphonuclear leukocytosis; there is no evidence of oral sepsis, of tonsillitis, of paranasal sinusitis, of cholecystitis, or of prostatitis. The search should, however, be continued further. There are, it is true, signs of chronic bronchitis, and it is barely possible that this may account for the leukocytosis that puzzles us.

There is no evidence that we have been dealing with blood crises in this patient, nor has he suffered any marked hemorrhages.

Biermer's anemia may be suspected when it does not exist; among the other anemias with which it may be confused I might mention: (1) The anemia that accompanies carcinoma of the stomach or carcinoma of the colon; (2) the anemia of chronic gastritis; (3) the anemia of cirrhosis of the liver; (4) the anemia accompanying endocarditis lenta; (5) the anemia of chronic nephritis; (6) the anemia that sometimes accompanies Addison's disease of the suprarenal glands; (7) the anemias that are associated with profound undernutrition from any cause; (8) the anemia of sprue, and (9) acute aplastic anemias.

Thus far in this patient we have not been able to make out the existence of any one of the possibilities mentioned. There may have been a chronic gastritis in this patient and he is certainly markedly under-

nourished, though it seems scarcely possible to me that these conditions could have given rise to the clinical picture that we have before us.

Though in clinical medicine we always try to arrive at precise diagnoses, we must ever be careful not to push our diagnostic conclusions further than the facts that we accumulate warrant us in going. Where any room for doubt exists, it is best to keep the mind open and to be satisfied with a "probable" diagnosis, pending the securing of data that remove all doubt, rather than dogmatically to assert finality of diagnosis!

TREATMENT OF THE PATIENT

I should treat this patient as though he were, in reality, suffering from the malady that we think most probable, namely, Biermer's anemia; it will be interesting to observe the effects of administration of liver and of liver extract. If he really has pernicious anemia, I should expect the reticulocytes in the blood to increase in numbers promptly, within one week, particularly if enough liver and liver extract be given. Failure of the blood to recuperate in true pernicious anemia is nearly always due to an underdosage of liver or of liver extract. If after a few weeks of liver therapy (full dosage) there is no marked improvement one should be doubtful of the diagnosis of pernicious anemia, or at least should search for some unsuspected complication. I have seen a number of cases in which the progress was but slow and discouraging on the ordinary dosage of liver daily, whereas on addition of more liver or of two or three vials of liver extract (No. 343, N.N.R.) to the average initial dosage of five or six vials, the blood promptly began to regenerate and a normal red count quickly reappeared. I should not hesitate to give to this patient seven, eight, or even ten vials of liver extract a day, dissolved in water and orange juice, in addition to some cooked liver. The reticulocyte count should be followed daily for a time and the number, size, and shape of the red cells should be carefully watched. After the blood count has approached normal, four vials per day (sometimes two vials daily) will usually suffice as a maintenance dose. The disease is not cured, but the blood count can probably be kept normal by this liver therapy. A second important therapeutical indication in this patient lies in the undernutrition; he should be forced to gain weight rapidly, for he is 28 pounds below his calculated ideal weight. With this in view much rest should be provided for, as well as an abundant food-intake of high caloric content, the ration, of course, being kept well balanced as regards protein, carbohydrates, fats, vitamines, and mineral salts. He should gain at least 15 or 20 pounds during the coming three months. It may be that one or two courses of subcutaneous injections of cacodylate of soda would favor a gain in weight. I prefer to give cacodylate of soda rather than Fowler's solution, since the latter sometimes disturbs digestion. If the arsenic had to be given by mouth, I should give it in the form of one of the organic preparations, like

elarson, which can be taken without disturbance of the gastro-intestinal tract. An injection of 8 or 10 units of insulin immediately before the principal meal of the day will often aid greatly to compel a rapid gain in weight in an undernourished patient.

Of course, it goes without saying that this patient should also take full doses of dilute hydrochloric acid (at least 1 dram) in aerated water at each meal time. He should be much out-of-doors in the sunshine, and if he has to live in a climate where there is but little sun, I should recommend systematic exposures to ultraviolet light.

The treatment of pernicious anemia by splenectomy has been abandoned since the advent of the liver therapy of Minot and Murphy. Even transfusions of blood, formerly our sheet-anchor, can, as a rule, be dispensed with.

The Ménière symptoms should be watched, and if they recur and are troublesome, sodium bromide or small doses of barbital might be helpful.

Due attention should be given also to the condition of the heart and blood vessels. The chronic bronchitis might be helped by suitable inhalation therapy.

The other members of this patient's family should be examined for achylia gastrica and for pernicious anemia, since these maladies are sometimes heredofamilial in incidence.

I shall be very much interested in hearing, later on, from Dr. Kruse as to the progress of this patient and, particularly, whether or not further observations throw any light upon the meaning of the atypical features of the anemia. I think it probable that this man will make a good recovery, though he may be compelled to continue the use of hydrochloric acid and of liver therapy indefinitely.

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PROFOUND SECONDARY ANEMIA WITH SPLENOMEGALY (BANTI'S SYNDROME) IN A PATIENT WHO HAS HAD BLEEDING INTERNAL HEMORRHOIDS FOR A YEAR, AND A HISTORY SUGGESTIVE OF GASTRIC ULCER FOR FIFTEEN YEARS AND WHO NOW HAS ACHYLIA GASTRICA AND A FILLING DEFECT AT THE PYLORUS, WHICH HAS CAUSED SUSPICION OF THE EXISTENCE OF CANCER OF THE STOMACH. DISCUSSION OF DIAGNOSIS AND THERAPEUTICAL MANAGEMENT[1]

WE have here a patient who presents some very great difficulties in differential diagnosis, for you will agree with me, I think, after hearing the history and the clinical findings, that there are some features of the case that are very puzzling indeed. I shall ask Dr. Paul Michaels to give you a brief summary of the clinical data that have been accumulated, after which I shall take the opportunity of discussing *seriatim* the more significant findings.

CLINICAL HISTORY (SUMMARIZED BY DR. PAUL MICHAELS)

The patient, Charles B., a Canadian of English stock, forty-two years of age, is a patient on Dr. McVey's service in Ward A of the Oakland Hospital.

His **chief complaints** on admission were of "rectal hemorrhage, weakness, shortness of breath, dizziness, nervousness, and loss of weight."

Past History.—The patient was on active service during the World War, was gassed in 1915, received gunshot wounds in the left hand, left shoulder, and axilla, and suffered a large shrapnel wound of the right hip. He has been a semi-invalid ever since the war. Before the war his appendix was removed (in 1910). During the war he gave a history that was very suggestive of gastric ulcer, inasmuch as for fifteen years he had epigastric pain and nausea during or directly after meals, these symptoms being relieved by vomiting or by taking soda. He was often awakened at night by pain, which could be relieved by alkalies. He has, however, before the present illness, had no blood in his stools, observed no tarry stools, and never vomited blood.

Family History.—This throws no light upon the case.

Present Illness.—The patient has been inclined to date the beginning of his illness to the time when he was gassed in the war. For fifteen years thereafter he had the symptoms of ulcer of the stomach mentioned. During the past year, however, he has had frequent rectal hemorrhages; he first noticed traces of blood in the stools and, later, there was dripping of blood and passage of clots during defecation. This bleeding from the rectum occurred without change in his bowel habits and was not accompanied by pain. He is very definite in his statement that the stools have never been tarry in appearance but have always been bright red. During the past three months he has grown steadily weaker, has become very short of breath, is often dizzy, feels very nervous and has lost 25 pounds in weight.

[1] Case presented at a Clinic held before the Alameda County Medical Society at Oakland, California, on Monday evening, December 16, 1929.

Physical Examination.—Marked pallor, scars of bullet wounds over the body; left femoral hernia, enlargement of the spleen; soft systolic murmur over the heart, apparently of hemic origin; normal blood pressure; dental caries; pilonoidal sinus; and, on proctoscopical examination, internal hemorrhoids with two bleeding points.

Laboratory Data.—*Blood.*—Red blood corpuscles 3,050,000; hemoglobin 27 per cent; white blood corpuscles 5550; differential count showed 60 per cent polymorphonuclear neutrophils, and 34 per cent of small mononuclears. In the stained smear, there were many hypochromic cells and there was obvious anisocytosis and poikilocytosis.

The *stools* contained bright blood, but no ova or parasites.

The *urine* was negative for albumin, sugar, and pus.

The *fragility test* of the red corpuscles yielded practically normal results, though the resistance to hypotonic solutions was perhaps slightly diminished. The calcium content of the blood serum was 10.4 mgm. per 100 cc. The bleeding time was three and a half minutes. The coagulation time five and a half minutes. Platelet count 186,000. Wassermann negative. No malarial parasites present in the blood.

The *stomach contents* were tested with administration of histamin by the method of Bloomfield and it was found that no free hydrochloric acid was present. The highest level of total acidity was 6 acidity per cent. The volume of gastric juice secreted was much diminished.

x-Ray Examinations (Dr. W. H. Sargent).—Lung fields are clear. Diaphragm moves freely. Heart and aortic arch are normal.

The stomach is in normal position; lower border slightly below the iliac crest. Walls of stomach soft and pliable, except in the prepyloric region where the upper side of the antrum appears to be indurated. A filling defect is constantly present at the pylorus and on the pyloric side of the duodenal cap; this area is extremely tender. The gastric walls are otherwise regular in outline and are normally movable. Peristaltic waves do not, however, develop very well; they pass through to the area mentioned above, but cannot be seen to pass further. The pylorus does not fill out well. The barium meal passed through in very small masses. The cap was not distinctly visualized.

At the end of six hours, there is a small fleck of barium in the stomach; the head of the meal is entering the transverse colon; the greater portion is in the terminal ileum.

At the end of forty-eight hours, the meal is distributed throughout the colon. Cecum in normal position, not freely movable. The tip of the cecum corresponding to the site of appendix operation is extremely tender. The transverse and descending portions of the colon are normally movable; no evidence of dilatation, of obstruction, or of new growth.

Conclusion.—There is definite pathologic alteration of the stomach in the prepyloric region. This has some of the appearances of a benign polyp, but the extreme tenderness and the peri-induration of the gastric walls make one very suspicious of new growth. The extreme tenderness of the cecum suggests chronic inflammation in the region of the former site of the appendix. There are no findings to suggest the source of the bleeding. Nothing abnormal can be seen in the colon above the sigmoid. We are not positive of the condition below the sigmoid. A proctoscopic examination is necessary to rule out disease of this portion of the bowel. Gallbladder visualization yielded a normal result. A barium enema was negative save for a moderate degree of colitis.

DISCUSSION OF THE CLINICAL DATA

This interesting account of the patient that we have just heard from Dr. Paul Michaels is now before us for consideration. Let us consider, first, the rectal hemorrhages, next the anemia, then the splenomegaly, and finally the condition in the stomach.

The Rectal Hemorrhages.—This patient has been passing bright blood from the rectum for a year. It seems that he consulted a physician at one time because of his anemia and told him of the hemorrhages from the rectum. Apparently no rectal examination was made at that time, but an iron tonic was given to him in order to improve the condition of his blood.

The blood passed has always been, as I have said, bright red, never tarry. This indicates, of course, an origin of the bleeding low down in the gastro-intestinal tract, for no matter how rapidly the contents of the gastro-intestinal tract may pass through, it is scarcely conceivable that blood from higher up, say from the stomach, the duodenum, or even the upper colon, could have been continuously bright red when passed per rectum.

On protoscopical examination in this hospital the rectum showed internal hemorrhoids and two definite bleeding points. It seems reasonable to believe, therefore, that bleeding internal hemorrhoids could account for the rectal hemorrhages of which the patient has complained.

The Profound Secondary Anemia.—You must have been impressed by the ghastly pallor of this man and you have heard that there is only 27 per cent of hemoglobin in the blood and that the red cell count is around 3,000,000. The color index is, therefore, very low, about 0.4. He has anisocytosis and poikilocytosis, but there is no outspoken megalocytosis. The individual red corpuscles show marked achromia rather than the hyperchromia that one sees in a primary anemia. This man's blood has all the earmarks of a profound secondary anemia. The leukocyte count shows neither leukocytosis nor leukopenia and the differential count exhibits no extraordinary features, though there is apparently a slight relative increase in the small mononuclear elements. The platelet count of 186,000 shows that there is no marked thrombocytopenia. We are not dealing with a hemolytic anemia, for there is no marked increase in the fragility of the red cells. The patient has no hemophilia, for his coagulation time is normal. He has not one of the purpuric diseases, for his bleeding time is normal and the platelet count is fairly high. Moreover, there seems to be no calcium deficiency in the blood and the prothrombin time is within normal limits. Obviously, therefore, there is nothing definitely wrong with the coagulation factors of the blood to account for frequent hemorrhages. A possible predisposition toward gastro-intestinal hemorrhage may, perhaps, be found in the enlargement of the spleen (to be immediately discussed).

The Splenomegaly.—I have just palpated this man's spleen and I find it to be very large indeed. You may recall that a spleen, in order to be palpable, must be two or three times its normal size. This man's spleen is not only palpable, but its tip extends at least three fingers' breadth below the left costal margin, which indicates a very marked enlargement of the spleen, though, of course, not nearly so great an enlargement as one sees in some leukemias.

What can be responsible for this enlargement of the patient's spleen? He has never had malaria. He has no leukemia. His Wassermann is negative. There are no signs of tuberculosis in the body, nor are there any signs of Hodgkin's disease. The occurrence of splenomegaly with marked anemia of the secondary type in a relatively young person places the patient in the group of cases long known as "Banti's disease," but now preferably referred to as "Banti's syndrome," since it has been shown that there is no unitary disease responsible for the cases that were described by Banti. A large number of different conditions can give rise to the clinical picture of Banti's syndrome. You will recall that in this syndrome there is often a marked tendency to gastro-intestinal hemorrhages and one wonders whether or not this man's persistent bleeding from internal hemorrhoids could be connected in any way with the splenomegaly of a Banti syndrome. The possibility should, I think, be kept in mind, though internal hemorrhoids may, as you know, bleed in the entire absence of Banti's disease.

The Gastropathy.—This man has had symptoms referable to his stomach for the last fifteen years. You have heard that he has had epigastric pain and nausea during or immediately after meals, relieved either by vomiting or by the taking of soda. He would often awake in the night because of pain that could be relieved by alkalies. Despite this long history that Dr. Michaels has referred to as a "typical peptic-ulcer history," he has never had hematemesis and has never had tarry stools.

If we knew nothing about the case except this long history of gastric complaints we might be inclined to rule out cancer of the stomach almost immediately. It is very rare, indeed, for cancer to develop in persons who have had a long history of gastric disturbance. On the contrary, patients who develop cancer of the stomach are usually patients who have had a particularly sound digestion; many of them tell you that they could "eat bricks" without trouble. Then, abruptly, a few weeks or months before they consult a physician, they begin to have gastric disturbances of one form or another, and, particularly, a dislike for meat, along with pain, nausea and, perhaps, gaseous eructations. The history of the latter sort, appearing abruptly in a patient whose stomach in earlier life has been very sound, should always excite the suspicion of a developing neoplasm.

It must not be forgotten, however, that there are some patients who give a long history of gastric disturbance suggestive of ulcer and who do actually develop carcinoma later. This is particularly true when carcinoma develops at the site of an old gastric ulcer (so-called *ulcus carcinomatosum*). A distinguished British surgeon, Moynihan, has asserted that patients with cancer of the stomach belong to either one of two groups: a principal group made up of patients who have always had a sound digestion and then suddenly began to show symptoms; and a

minor group consisting of patients who have always had "weak stomachs." On the whole, the anamnesis of this patient would make one much more suspicious of gastric or duodenal ulcer than of carcinoma of the stomach.

Ulcer of the stomach is, however, associated nearly always with hyperacidity of the stomach juice and sometimes with an increased volume of a gastric secretion, whereas carcinoma of the stomach is associated with absence of free hydrochloric acid, except in the cases of ulcus carcinomatosum in whom free acid may persist for a time after the carcinoma develops. Now you have heard that this patient has an achylia gastrica; he has no free hydrochloric acid in the stomach contents, and the volume of the secretion as tested by Bloomfield's method (after histamin) is markedly diminished. These are findings that are more in accord with the idea of carcinoma of the stomach than with that of ulcer. It is possible, however, that this man has always had an achylia gastrica, for there are certain persons who are achylic from birth, and such persons are prone to develop pernicious anemia and subacute combined degeneration of the spinal cord. We cannot be sure, however, that this person has a constitutional achylia nor whether he has developed achylia because of a long-continued chronic gastrititis. Ulcer of the stomach may occur in patients who are achylic, and, again, a patient with an old ulcer and an accompanying chronic gastritis may develop an achylia after a previous period of hyperchlorhydria.

The persistence of epigastric pain and of nausea in this patient over so long a period is strongly suggestive of some organic disease of the stomach and is very much against the idea of any merely functional disturbance of the stomach. The recent loss of weight naturally makes one apprehensive of a neoplastic development.

We, therefore, turn to the *x*-ray findings with deep interest, and, as you have heard, they are positive. They reveal a filling defect at the pylorus, a defect that involves both the stomach and the adjacent portion of the duodenum. There appears also to be some induration of the wall of the stomach at the upper margin of the antrum of the pylorus and this region is tender on palpation. Peristaltic movement is arrested as this area of apparent induration is approached. These signs could be due to an old ulcer with inflammatory infiltration of the adjacent stomach wall; or they could be due to a benign lesion like a polyp; or they may be due to a carcinoma of the stomach. The roentgenologist, Dr. Sargent, was inclined to the opinion that he had to deal with a malignant neoplasm.

DIAGNOSTIC CONCLUSIONS

If you were to ask me to summarize my diagnostic conclusions on the data accumulated, I should make mention of the following:

1. Chronic gastropathy, with achylia gastrica, epigastric pain, nausea, loss of weight, filling defect at the pyloric end of the stomach and adjacent

portion of the duodenum with apparent induration of the antrum pylori, and an arrest of peristalsis in the same area occurring in a patient who has given a history of probable ulcer of the stomach for the preceding fifteen years. (Probably carcinoma ventriculi, possibly benign neoplasm like polyp, or, possibly, indurated ulcer.)

2. Internal hemorrhoids (bleeding) and chronic colitis (distal).

3. Very severe anemia of the secondary type, 27 per cent of hemoglobin and a color index of 0.4 and with marked splenomegaly (keep thrombosis of splenic vein in mind).

4. Pericecal inflammation at the site of the appendix that was removed.

5. Femoral hernia, left.

6. Pilonidal sinus.

FURTHER MANAGEMENT OF THE CASE

Though we have come to some positive conclusions, you will observe that there is still some doubt as to the precise nature of the lesion at the pyloric end of the stomach and there is also some doubt as to the nature of the malady that underlies the particular Banti syndrome that exists in this patient.

As physicians, we have, sometimes, to intervene therapeutically in the absence of complete diagnostic knowledge. But we do know enough about this patient to lead us immediately to act.

Obviously, the first therapeutical indication here is to stop the bleeding from the rectum and that should be a matter of easy accomplishment provided we are dealing simply with bleeding internal hemorrhoids and not, in addition, with some obscure disposition of an especial nature to gastro-intestinal hemorrhage (such as is sometimes met with in connection with Banti's syndrome). Any skilful proctologist will know the best way to deal with these bleeding internal hemorrhoids. I suppose the bleeding could be stopped by injections of quinine and urea, by injections of carbolic acid, or by cauterization through the proctoscope. I personally would call a skilful proctologist to my aid if I had charge of the case and I should give him a free hand to deal with the internal hemorrhoids as he saw fit, provided, of course, that he did not undertake any operation such as removal of the pile-bearing area of the patient.

After stopping the rectal hemorrhage the next indication for therapy will be to overcome the secondary anemia as promptly as possible. When the hemoglobin has fallen as low as it is in this case, and when the bleeding that is probably responsible for this has been going on for a year, it is quite possible that the blood will not quickly recuperate even if further hemorrhage be prevented. I should, therefore, in this case, have the patient's blood tested to see in what group his blood falls and then seek a suitable donor, or donors, and give him a transfusion every four

or five days until the hemoglobin of his blood is up to 85 per cent or higher. This will make the patient look and feel like a different man.

But after the rectal hemorrhages have been overcome and the secondary anemia has been combated by transfusions and by hematinic drugs, we have further to decide what we shall do about the stomach and what we shall do about the spleen.

Since the patient has achylia gastrica, it would seem desirable to give him full doses of diluted hydrochloric acid three times a day. I should give him at least a teaspoonful of the dilute acid in aerated water with each meal.

It would next seem to me to be important to recheck the roentgenological findings by means of another fluoroscopical examination and another series of gastro-intestinal plates. If the findings should be practically the same as at the last examination I should be inclined to request a skilful surgeon to perform an exploratory laparotomy; if he should find a carcinoma of the stomach and if it should prove to be operable in the sense that there are no metastases or only very small regional metastases I should advise a resection of the stomach by the second method of Billroth. If the stomach should be noncarcinomatous and only an old ulcer or a benign neoplasm should be found, I should want the surgeon to deal with what he found according to his best judgment.

The only other question that would come up would be with regard to the splenomegaly. Should one attempt to remove the spleen in this patient? It would seem to me that the situation with regard to the pylorus is more important than the situation with regard to the spleen. If a benign condition of the stomach should be found and could be treated adequately surgically, one might, I think, run the risk of leaving the spleen in, unless the surgeon thought it were feasible to remove it at the same operation. If it were left in, and the patient did well after his gastric operation, one could leave the spleen alone unless there were a recurrence of the hemorrhages. Naturally, one would ask the surgeon to inspect the liver carefully at the operation to make sure that an atrophic cirrhosis of the liver was not developing, for sometimes an early cirrhosis of the liver that has not caused ascites can give rise to a considerable enlargement of the spleen; I have seen one such case recently in San Francisco.

If the surgeon should unfortunately find not only carcinoma ventriculi but also a development of the carcinoma or metastases that made radical removal hopeless, I would have the surgeon do as little as possible within the abdomen, closing it up at once. In that event, after recovery from the operation, I should tell the patient that the treatment in his case from now on was to be medical rather than surgical, and I should institute an active campaign of therapy, never letting the patient know how hopeless his condition was. I should not want his wife to know, but I should want some male relative to be told (in strict confidence) the exact

situation. There are men who think that they can face anything in this world but, in reality, there are very few men who can easily live without hope. Even the most philosophically minded man ought to be protected from a hopeless prognosis. It is the duty of the medical man, therefore, in cases of hopeless cancer of the stomach, to do everything in his power to ameliorate the condition of the patient, to maintain as much strength as is possible, and, especially, to prevent pain and discomfort as far as lies in his power.

In the medical therapy, I should try to make sure that I did the patient no harm, but I should see him regularly and I should keep him convinced that I was working along some definite plan of treatment that was designed to help him. The diet could be carefully prescribed; one could continue to give hydrochloric acid after meals; for the vomiting one could give a drop of tincture of iodine, well diluted with water, occasionally; and for the pain and discomfort one could use at first codeine and, later, Schlesinger's solution (morphine, dionin, and scopolamine).

Some years ago I found the formula of Schlesinger's solution in a small journal published in Vienna and thought that I would give it a trial. It worked so admirably in painful conditions, and particularly in the pain of malignant neoplasm, that this solution soon came in common use in the Johns Hopkins Hospital and, gradually, its use has spread over the country. The formula of Schlesinger's solution is as follows: ℞ Scopolamine hydrobrom. 0.0025, morphine mur. 0.2, dionin 0.4. distilled water 10.0.

Sig. For hypodermic injection five to eight minims or more, to be injected as required.

When one first begins to use Schlesinger's solution for the relief of pain, 1 dose of 5 minims at 9 P. M. will usually suffice. Later, the evening dose must be increased perhaps to 7 minims or even more and a morning dose of 5 or 7 minims may be given. Later on, in carcinoma cases, one may have to give 3, 4, or more doses each day and the dosage may be gradually slightly increased. Fortunately, this mixture relieves pain admirably, gives sound sleep, and does not cause the "dopiness" next day that is so common when morphine alone is used; instead, the patients have a slightly euphoric feeling on awakening in the morning. I know of no better euthanasic method for patients dying from carcinoma than the judicious use of this mixture. One of our Baltimore pharmaceutical firms is now supplying the active ingredients of Schlesinger's solution in tablet form, which makes its use much more convenient than formerly. I can recommend this scopolamine-morphine-dionin mixture to you most highly for the purposes mentioned. You will also find it very useful for many other pains that are so severe that morphine would ordinarily be resorted to for their relief.

Before passing on to the discussion of another patient I want to

emphasize the high degree of secondary anemia that may come simply from bleeding hemorrhoids. An anemia fully as severe as that presented by the patient whom you have seen could easily come from the recurrent rectal hemorrhages of a year's duration. One should never wittingly permit even small hemorrhages to recur frequently from any source. It would have been easily possible, I think, to have stopped the rectal hemorrhages in this man a year ago by simple methods. The same is true of recurring epistaxis; one should not allow patients to have nosebleeds too frequently. A careful inspection of the nasal mucous membrane will usually reveal the source of the bleeding, after which it can be rendered innocuous.

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ANEMIA WITH LEUKOPENIA, THROMBOCYTOPENIA, AND PURPURA IN A PATIENT WITH MARKED SPLENOMEGALY AND ENLARGEMENT OF THE LIVER, AND WITH A HISTORY OF RECENT GASTRIC HEMORRHAGE, AND PROBABLE THROMBOPYLEPHLEBITIS; COMMENTS UPON DIAGNOSIS AND TREATMENT OF THE PROCESSES MANIFESTED BY THE BANTI SYNDROME[1]

DURING the past few years our ideas regarding the maladies of younger patients who exhibit a marked anemia with leukopenia in association with enlargement of the spleen have been undergoing a rather marked change. It was customary to designate such cases as "splenic anemia"; but it was soon realized that the association of anemia with enlargement of the spleen and without increase in the leukocyte count represented merely a "symptom complex" or "syndrome" that was not confined to a single disease. It was then suggested that the use of the term, if justifiable at all, be reserved for the initial stage of "Banti's disease," a malady that was described as occurring chiefly in young adults and that was characterized by weakness, pallor, digestive disturbances, and enlargement of the spleen, with a tendency to profuse gastric hemorrhage (often fatal) and also to the development (in the later stages) of atrophic cirrhosis of the liver with ascites, jaundice, increasing anemia, and cachexia. This "Banti's disease" was not to be confused with the splenomegaly of hemolytic jaundice, with that of ordinary cirrhosis of the liver, or with the splenomegalies associated with chronic infections of recognized type (*e. g.*, malaria, syphilis, or tuberculosis). The performance of splenectomy as a therapeutical measure had a favorable effect in delaying the progress of Banti's disease, provided the operation could be undertaken before the liver became cirrhotic.

Unfortunately, the vagueness of the older term "splenic anemia" is not wholly avoided by limiting its application to the initial stages of "Banti's disease," for it has turned out that Banti's disease itself is no single disease entity, but is a conglomerate of maladies, any one of which can give rise to the clinical picture that one may, if he desire, call the "Banti syndrome."

Banti, himself, in attempting to isolate a single malady from the group of very chronic splenomegalies associated with anemia in which the etiology was not clear, set up the following criteria for a disease that he believed to be due to primary alterations in the spleen: (1) An

[1] Clinic held by invitation in Lane Hall at the Stanford University Hospital, December 13, 1929.

anemic stage of several years' duration, accompanied by a smooth, enlarged spleen, normal white blood count, and occasional febrile attacks; (2) a *transition stage* of several months' duration, in which gastrointestional symptoms became prominent and the patient became jaundiced; and (3) an *ascitic stage* with jaundice and fever, without leukocytosis, but with severe anemia continuing for six to twelve months and often terminating fatally through severe gastric or intestinal hemorrhage. At autopsy, he described sclerosis of the splenic blood vessels, disappearance of the malpighian follicles of the spleen, owing to fibro-adenosis, induration of the splenic pulp, marked sclerosis of the portal vein, and moderate interlobular cirrhosis of the liver, with absence of alterations in the lymph glands of the body.

It was Banti's opinion that the spleen became a source of chronic intoxication, the splenic poisons causing endophlebitis of the splenic veins and, later, of the portal veins and degeneration of the liver. The improvement that, in many instances, followed upon early removal of the spleen lent support to his conception of etiology and pathogenesis.

After a personal experience with 50 cases, Banti admitted that the first (anemic) stage sometimes failed to appear, that the second stage (in which the liver was large, the skin was of a dirty yellow tinge, and the urine contained urobilin) might last much longer than eighteen months, and that, in the third stage, the clinical picture might be identical with that of an atrophic cirrhosis of the liver due to chronic alcoholism. He came to believe that the splenic disease had its origin in some toxic or infectious agent that reached it through the arterial blood, and that the spleen then produced toxic substances that injured the portal vein and the liver; timely removal of the spleen prevented the secondary liver disease or retarded its development, as proved by thirty-six splenectomies that were followed by cure in twenty instances.

Though Banti has found a number of supporters of his view (notably in Eppinger, Grawitz, and Umber), the majority of clinicians and of pathologic anatomists who have studied the subject intensively have declined to accept it. Thus, from the histologic side, Mennet (1920) denied the constancy and the specificity of the changes in the spleen described by Banti; and Marchand and Chiari have maintained that no clear distinction between the cirrhosis of Banti cases and ordinary cirrhosis has been established. In the earlier literature some cases of Gaucher's disease and of the Niemann-Pick disease were, doubtless, included under the name of "Banti's disease." Later on, several pathologists proved that spleens wholly similar to Banti's spleens could arise secondarily as a result of chronic pylephlebitis. From their clinical studies, Naegeli, Minkowski, and others have denied the existence of any unitary malady as responsible either for the clinical syndrome or the pathologic changes. Dr. Ophüls tells me that some of the cases of iron and lime incrustation of the spleen associated with anemia, sometimes spoken of also in the

literature as "mycosis" of the spleen, may have been classed in the Banti group. Accordingly, at the present time, the term "Banti's symptom complex" is utilized simply as a convenient appellation for a syndrome that may be due to any one of several different disease processes, the precise nature of which cannot always be determined *intra vitam.*

The patient that Prof. Arthur L. Bloomfield has selected for the clinic today, presented, on entry to the ward, a clinical picture that corresponded to the Banti syndrome, for he was anemic, had a very large spleen, with enlargement of the liver, and had just suffered from profuse hematemesis. He is now being carefully studied, in the medical ward, both from the physical and the laboratory side. We shall hear first a summary of the results of the examinations thus far made by Dr. Barnett and Dr. Sumner, and by the clinical clerk, Mr. Jacobs.

SUMMARY OF CLINICAL HISTORY

The patient, Robert H., age forty-seven years, a single, white man, by occupation a hospital porter, was admitted to the Stanford University Hospital with the *complaint* that he had vomited blood one hour before entry.

History of Present Illness.—Four days before admission, he awoke feeling chilly and found that he had fever. The fever and the chilliness persisted, without other symptoms except general malaise and some increase in an old nasal discharge. On the morning of entry, he had felt that he had recovered and had gone back to work, feeling quite well, when he suddenly became weak and dizzy and slipped to the floor. On being helped into an ambulance, he was nauseated and vomited a cupful of fresh blood, after which he felt somewhat better again.

Previous History.—The patient has suffered from chronic paranasal sinusitis for many years. In 1920 a submucous resection was done; and in 1923 the frontal and the ethmoidal sinuses were drained through the nose. In 1924 radical operations were done upon the frontal sinuses and upon the antra on both sides. Accompanying the continued nasal discharge he had dizziness and headaches. In 1928 and again in 1929 he had further operations upon the left frontal sinus. He asserts that, by these operations, his headaches and dizziness have been entirely relieved, but, notwithstanding, he continues to have nasal and postnasal purulent discharge.

Some six years ago, he had an attack of pain in the right upper quadrant of the abdomen, which lasted only one day. *x*-Ray examinations made at this time, however, revealed no definite abnormalities in the gallbladder or the gastro-intestinal tract.

In the year 1908 (twenty-one years ago), he had a chancre and was treated for four years for syphilis, receiving a large number of arsphenamine injections as well as mercurial treatment and iodide of potassium. Since then, his Wassermann reaction has been repeatedly negative, and it is still negative. He never had bleeding in earlier life.

On **physical examination,** he was found to be a well-developed and well-nourished man. Skin and mucous membranes pale. Pupils normal. Many crowned teeth that have not been investigated recently. Tonsils small. Postnasal discharge still present. Chest of the asthenic type. Lungs negative. Heart not enlarged. No heart murmurs. Blood pressure—90 systolic, 60 diastolic. Abdomen slightly distended and tender on palpation. Liver very much enlarged, firm and irregular, the liver edge being felt a full hand's breadth below the costal margin in the mammillary line. The spleen can also be felt three finger's breadth below the left costal margin. A purpuric rash can be seen over an area the size of one's palm, on the right lower leg.

The temperature on admission was 36.8 C., the pulse rate 90, and the respiratory rate 16.

On **laboratory examination,** the results were as follows: *Blood:* Red blood corpuscles 2,920,000; hemoglobin 54 per cent (Sahli); white blood corpuscles 3900. Differential count: Polymorphonuclear neutrophils 50 per cent; small mononuclears 44 per cent; monocytes 6 per cent; eosinophils 1 per cent. Platelets 6400. Clotting time, three minutes; bleeding time, two minutes. On examination of the fresh blood slide, an occasional poikilocyte could be seen, but there was no marked anisocytosis and, especially, no obvious megalocytosis. In stained specimens, there was some polychromasia of a few of the red cells. Only one normoblast was seen in the examination of many slides. Fragility test was normal. Icterus index 5.6. Van den Bergh test: direct, negative; indirect, 0.3 unit.

Urine.—Negative except for the presence of many hyaline and granular casts and a trace of albumin.

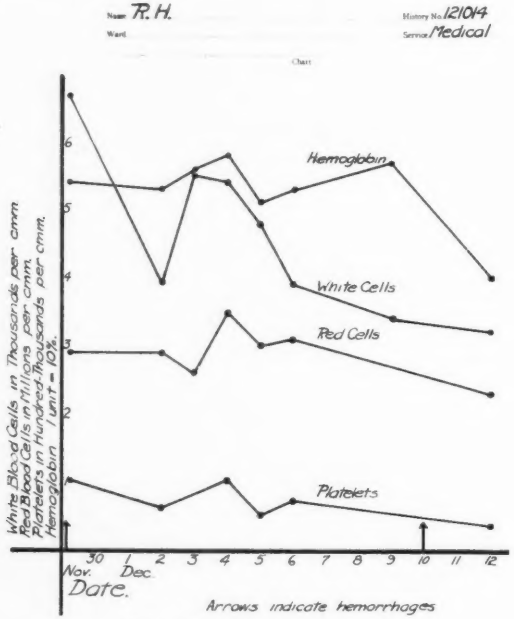

Fig. 4.—Anemia with leukopenia.

Feces.—Contained much red and black blood.

Wassermann reaction, repeated, was found negative.

Course in the Hospital.—The patient was kept quiet in bed and he soon felt very much better. During the first two days he was given nothing by the mouth. Then, small amounts of milk were permitted. After the fourth day, he was given liquids and, later, a soft diet. The blood count remained about the same and the blood disappeared from the stool.

During the night of December 10th, the patient awoke with pain in the abdomen and marked distention. On physical examination, it was thought at first that the distention might be due mainly to gas, but on passage of a rectal tube it was soon found that gas did not account for it. On percussion it was found that a large effusion

into the peritoneal cavity had suddenly developed. Paracentesis was done and about 2 liters of clear, straw-colored fluid removed; this fluid had a specific gravity of 1.008. The cells found in the ascitic fluid were chiefly small mononuclears along with some peritoneal endothelial cells. The fluid was obviously a transudate rather than an exudate.

On the day following this acute and diffuse distention of the abdomen, the stools were again loaded with tarry blood, showing that the patient had suffered further hemorrhage into the gastro-intestinal tract. The anemia, the leukopenia, and the thrombocytopenia became much more marked. (See accompanying chart, Fig. 4). It has been necessary to keep the patient very quiet, and further *x*-ray examinations have not been thought advisable as yet.

Further studies of the blood showed that the individual blood platelets were not markedly altered in appearance; no giant forms and no very minute forms were observed. The coagulation time and the bleeding time were again tested and were found to be within normal limits. The Rumpel-Leed test for diminished capillary resistance showed that no purpuric spots appeared after the removal of the tourniquet. The fibrinogen content of the blood has not been determined yet, nor has the Lee-Vincent test for calcium deficiency yet been applied. The prothrombin time, tested by Howell's method, was found to be normal. The blood clot that formed in blood removed from the vein showed good retractility.

The average diameter of the red blood cells has been determined by means of Eve's halometer (kindly supplied by Dr. Cheney); though the average diameter of the red cells is at the upper limit of normal, there is no evidence of megalocytosis pointing to pernicious anemia.

The eye signs and the bone signs of Gaucher's disease are absent.

DISCUSSION OF THE CLINICAL FINDINGS

You have heard this interesting history of a man, who, aside from his earlier infections, has felt very well, indeed, up to fourteen days ago, when he suddenly had a hemorrhage (vomiting of blood; appearance of blood in the stool). This hemorrhage was accompanied by nausea, vomiting, faintness, and great weakness, requiring his immediate removal to the hospital ward. Examination revealed a pronounced anemia, purpuric spots on one leg, marked enlargement of the spleen and of the liver, the latter being firm and nodular. After a few days of improvement he had sudden pain in the abdomen with marked distention; this was accompanied by the abrupt appearance of ascites and by another hemorrhage that increased the anemia. Let us now consider, in a little more detail, the principal features of this malady and try to interpret their significance.

The Hemorrhagic Tendency.—This man has had two profuse hemorrhages from the gastro-intestinal tract; he has also shown purpuric spots on the skin, though these have disappeared since he entered the hospital. We must now consider the origin of the hemorrhage into the gastro-intestinal tract and of the purpura. Why has he exhibited this hemorrhagic tendency? Has he been bleeding from an erosion or an ulcer somewhere in the upper gastro-intestinal tract, or has there been merely oozing from the mucous membranes. We know that, in connection with the Banti syndrome, gastro-intestinal hemorrhages are quite common. Sometimes they are due to oozing from the mucous membranes

because of acute congestion and impaired coagulation capacity of the blood. Sometimes they are due to ruptures of esophageal varices secondary to a cirrhosis of the liver that has already developed. This man has an enlarged hard liver and it is possible that the cirrhosis of the liver has caused some portal obstruction with development of esophageal varix, erosion of which might have caused a hemorrhage.

The finding of purpura also leads us to consider the coagulation factors of the blood.

I understand that this audience is composed mainly of third- and fourth-year medical students who are not far removed from the regular work in the physiologic laboratory. You have there become familiar, doubtless, with the details of the process of blood coagulation and with the factors upon which coagulation depends. It might, however, be well for you, after the clinic, to reread the chapters in your text-book of physiology upon blood coagulation, and, if you can give the time to it, you might also read the Harvey Lectures by Professor Howell, delivered in 1916–1917, upon this subject.

You may recall that the factors essential for normal coagulation of the blood are: 1. A normal fibrinogen content of the blood (about 0.4 per cent). This fibrinogen is derived from the liver; in certain severe diseases of the liver the coagulation time of the blood is prolonged and a flimsy clot may form, owing to diminution of the fibrinogen content of the blood.

2. A sufficient supply of ionizable calcium salts. Faulty coagulation in chronic obstructive jaundice is often due to calcium deficiency. You can easily test for such calcium deficiency by the simple method of Lee and Vincent.

3. A normal prothrombin content of the blood. Fibrin is formed by the action of thrombin, formerly known as "fibrin ferment," upon fibrinogen. The thrombin, itself, is derived from prothrombin or thrombogen, which is derived from blood platelets.

4. A supply of cephalin (or thromboplastic substance). This cephalin is set free from tissue cells that are injured, or from disintegrating white blood corpuscles or blood platelets. Slowing of liberation of cephalin has been supposed to be the cause of the delayed coagulation in hemophilia.

5. A sufficient number of blood platelets. Deficiency of platelets is the commonest cause of spontaneous pathologic hemorrhage, for example, in essential thrombopenic purpura, and in the anemias due to aplasias of the bone marrow. The blood platelets are the main, if not the sole, source of prothrombin; they are also one source of cephalin; and their presence is sufficient numbers is esssential for normal retractility of the blood clot.

The five elements, just enumerated, are all essential for normal coagulation of the blood. The reason the blood does not coagulate within

the vessels under normal conditions, is because of the presence of antithrombin and of antiprothrombin. We have, however, but little knowledge, as yet, of an increase of these substances in pathologic states.

Now, in ordinary clinical work it would scarcely be feasible to estimate quantitatively the contents of the blood in all these substances by the exact method used by physiologists. In clinical work we have to learn how to take short cuts that will give us information that is sufficient for our purposes. And I may say, at once, there are a few simple tests that will give, in the majority of cases, sufficient information without the expenditure of much time or energy. These tests include (1) a platelet count; (2) a determination of the bleeding time; (3) a determination of the coagulation time; (4) observation of the retractility of the clot formed; (5) Lee and Vincent's test for calcium deficiency; and (6) the Rumpel-Leed test for decreased capillary resistance. As a rule, these few tests will suffice, though in certain instances it may be desirable to have, also, (7) an estimation of the fibrinogen content of the blood, and (8) a determination of the prothrombin time.

In our patient the blood platelets are markedly diminished in number; they were only 64,000 per c.mm. on admission and they have fallen since to a much lower level (36,000). Normally, there should be about 300,000 blood platelets per c.mm. The bleeding time has been tested and found to be normal. The coagulation time is within normal limits, and the retractility of the clot seems to be satisfactory. As yet no test has been made in this patient for calcium deficiency nor has the fibrinogen content of his blood been determined. The prothrombin time, however, is within normal limits.

We can be sure from the studies already made, then, that we are not dealing here with essential thrombopenic purpura (Werlhoff's disease), for the bleeding time is normal.

Nor are we dealing with a hemophilic patient, for he does not come from a family of bleeders, he has had no bleeding in earlier life, and, moreover, his coagulation time is within normal limits and the retractility of the clot is normal.

The hemorrhage in this patient, therefore, must be due to ulcer, to rupture of an esophageal varix, or to oozing from the mucous membranes from congestion. The purpuric spots that occurred upon the leg are probably to be associated with the low platelet count and the hypoplastic condition of the bone marrow. As the man has had no arthritis, we are not dealing with Schönlein's purpura, nor has he had the abdominal attacks suggestive of Henoch's purpura, so often met with in children.

Personally, I am inclined to think that the hemorrhage in this man is due either to an eroded esophageal varix, secondary to the cirrhosis of the liver or to severe congestion of the veins dependent upon portal obstruction from some other source. This point will be dwelt upon a little later. Ulcer and cancer are improbable, though roentgenograms of

the gastro-intestinal tract will be carefully studied when they can be made to rule out these causes of hemorrhage.

Leukopenia and Thrombocytopenia.—Though the patient tells me that he had noticed that he was growing somewhat paler, we have no record of examination of his blood preceding the occurrence of his gastrorrhagia. The hemorrage was so severe that he might easily have a post-hemorrhagic anemia and, undoubtedly, a part of his anemia is of this type. In post-hemorrhagic anemia, however, there is usually a leukocytosis; and there are also, very soon after hemorrhage, signs of active regenerative activity of the erythropoietic tissue of the bone marrow as shown by an increased number of reticulocytes, nucleated red blood corpuscles, and polychromasic cells. In this patient, there is no leukocytosis, but instead, a marked leukopenia with especial diminution of the varieties of the white blood cells that are derived from the bone marrow; moreover, there is very little evidence of active regeneration of red cells. Mr. Jacobs tells us that he saw only one normoblast in the many slides that he examined, that the reticulocytes have not exceeded 1 or 2 per cent, and that only a few polychromasic cells could be seen. There is clear evidence, therefore, that the activity of the bone marrow in this patient is depressed, that is to say, we have to deal, in him, with an aplastic or, rather, a hypoplastic condition of the bone marrow. The manufacture of new red cells (erythropoiesis) and the manufacture of new white blood cells (leukopoiesis) in the bone marrow are both below normal. The marked reduction of blood platelets, too, is evidence of depression of bone marrow activity. You will remember that the blood platelets have their origin in the pinching off of little bits of cytoplasm from the megakaryocytes (giant cells) of the bone marrow. This man's thrombocytopenia is increasing rapidly, as you have heard of the progressive reduction of the platelet counts. We have, therefore, before us a great deal of evidence that points to the existence of a hypoplastic bone marrow in this patient.

We can rule out, I believe, the Addison-Biermer type of anemia, despite the fact that there has been some anesthesia of the soles of the feet and in a girdle area about the abdomen. The anesthesia has now largely disappeared and the blood picture is not that of a primary anemia; owing to the history of vomiting of blood, it has not seemed wise to pass a stomach tube, so we are not informed as to the presence or absence of free hydrochloric acid in the stomach contents.

The Enlargement of the Spleen.—This man's spleen is very much enlarged. In order to palpate a spleen, it must be two or three times its normal size; but this man's spleen is not only palpable, but it is so much enlarged that its lower pole can be felt at least three fingers' breadth below the left costal margin; that means, that he has a marked splenomegaly. This spleen is too large and too hard to be an acute splenic tumor. We are, undoubtedly, dealing here with a chronic splenomegaly in which there has been much increase of the fibrous tissue

in the spleen. It is rather large to be the stasis spleen dependent upon portal obstruction, but it might be such a stasis spleen of unusual size. In marked portal obstruction of any origin (cirrhosis hepatis; thrombophlebitis of the portal system of veins), one may see considerable enlargement of the spleen. This is not the spleen of any form of leukemia nor of Hodgkin's disease, as has been proved by the studies of the circulating blood and by examination of lymph glands in different parts of the body; no general enlargement of lymph glands is to be made out.

The Enlargement and the Increased Consistency of the Liver.—This is a very large and a very hard liver and, on palpating its edge and its surface, I find it to be rough and coarsely nodular. Such an enlargement of the liver must be accompanied by an increase of fibrous tissue in the organ; in other words, we must here be dealing with a cirrhosis of the liver. Passive congestion can cause enlargement of the liver, but in this man there are no signs of cardiac failure. The large size of the palpable nodules in the liver makes one a little suspicious of the possibility of malignant neoplasm in the liver; and this possibility should not be lost sight of. I am inclined to think, however, that we are dealing with a non-neoplastic disease. This man has taken some alcohol, but not in large quantities. He has had, over a long period, a chronic infectious process in the paranasal sinuses. It is possible that we have to deal here with the coarsely nodular cirrhosis that accompanies certain chronic infections. I refer to the so-called "toxic cirrhosis" of Mallory. The rose bengal test has been applied in this patient and there is no abnormal retention of the dye in the blood. Indeed, if anything, there is a somewhat increased permeability of the liver to the dye, inasmuch as he is said to have eliminated 75 per cent of the dye at the end of sixteen minutes. If he had an ordinary atrophic cirrhosis of the liver of the Laënnec type, I should expect a marked retention of the dye. In nodular cirrhosis, there may be no retention in the earlier stages of the disease, but there is usually retention later. The cirrhosis of the liver is probably not of syphilitic nature as the patient's Wassermann reaction is negative.

The Abrupt Development of Outspoken Ascites.—A remarkable feature in this case was the sudden appearance of ascites a few nights ago in association with an acute attack of abdominal pain. This points to the sudden occurrence or at least to a sudden increase of obstruction in the portal system of veins. On inspection of this man's abdomen, I observe that a compensatory circulation is developing; the veins all over the surface of the abdomen are somewhat enlarged. There is also marked enlargement of the veins leading from the right inguinal region up along the right flank to the right axilla. This latter venous dilatation points rather to obstruction to the inferior vena cava and to a compensatory circulation between the inferior cava and the superior cava than to obstruction to the portal circulation,

whereas the general venous dilatation over the abdominal wall and particularly around the umbilicus points to portal obstruction with development of compensatory circulation between the portal system and the caval system. Marked ascites, even when due to portal obstruction, can, however, compress the inferior vena cava and cause dilatation of the lateral veins of the abdomen and thorax.

What, then, has been the cause of this suddenly appearing ascites? It is inconceivable that it could be due to sudden increase of connective tissue in the liver. On the other hand, the abrupt onset of the ascites in association with abdominal pain that awoke the patient in the night is highly suggestive of thrombosis of some large vein of the portal system. In the diseases underlying the Banti syndrome, it is common to have sclerosis of the veins and a certain amount of pylephlebitis. I think it probable that there has been a pylephlebitis in this patient and that he has had a thrombosis of at least some large branch of the portal system of veins; as a result of this thrombopylephlebitis, the sudden effusion of fluid into the peritoneal cavity seems to have occurred.

The Renal Disease.—This patient has a trace of albumin and many hyaline and granular casts in the urine. He, therefore, must have some "renal disease," in other words, some form of "nephropathy." There cannot, however, have been much interference with the glomerular functions for the blood pressure is very low, only 90 systolic. I do not think it probable that there is much renal insufficiency in this patient despite the fact that he has renal disease. Again, we have as yet no information regarding the nonprotein nitrogen content or the urea nitrogen content of the blood, though tests for these are soon to be made. The phthalein test and a Mosenthal test may throw additional light upon the nature of the nephropathy. It would seem probable that we have to deal here merely with a slight toxic-degenerative nephropathy, perhaps associated with the chronic paranasal sinus infection.

Diagnosis.—We are justified, therefore, in drawing the following diagnostic inferences in this patient:

1. Banti's syndrome with anemia, splenomegaly, cirrhosis of the liver, thrombopylephlebitis, gastric hemorrhage, hypoplastic bone marrow, and purpura.
2. Chronic suppurative paranasal sinusitis (with history of recent acute exacerbation).
3. Suspect teeth.
4. Suspect gallbladder (to be visualized later by *x*-ray examination).
5. Arterial hypotension (blood pressure, systolic 90, diastolic 60).
6. Toxic-degenerative nephropathy (with albuminuria and cylindruria).

TREATMENT OF THE PATIENT

The indications for the treatment of this patient would seem to be clear. In the first place, we must do everything possible to prevent

further hemorrhage. In the second place, we must try to overcome the anemia. In the third place, we must consider whether or not the spleen should be removed surgically in the hope of more permanent benefit.

For the *control of hemorrhage*, we must rely upon absolute rest and the avoidance of irritation of the gastro-intestinal tract. Further studies of the blood coagulation factors will be made, particularly with reference to calcium deficiency and if calcium deficiency be found, calcium will be administered in the form of calcium lactate, or, one may give 50 per cent of calcium chloride in milk or in soup. In some cases the injection of a sterile solution of gelatin (subcutaneously or intramuscularly) has been helpful; ampoules of 4, 10, and 40 cc. of a 10 per cent solution are now put up by the pharmaceutical houses. In hemorrhage from the stomach and intestines and in hemoptysis, the injection of 10 cc. of a 10 per cent sterile solution of common salt into a vein has been practically helpful in many cases. Or, one may give an intramuscular injection of from 10 to 20 cc. of human blood.

After the hemorrhage has ceased, we shall want to *overcome the anemia*. This patient's blood might be brought up by cautiously administered transfusions of whole blood, using preferably the direct method from donor to receptor. One or two transfusions per week might be given until the hemoglobin is above 85 per cent. Of course, a suitable donor should be chosen after determination of the blood group to which the patient belongs.

If we should be successful in arresting the hemorrhage and in overcoming the anemia by the methods mentioned, the question of splenectomy will next come up. Undoubtedly, many patients exhibiting the Banti syndrome have been greatly benefited by removal of the spleen. There is a very large surgical literature on this subject and I have selected some of the more important references to which you may refer. The patient, at the present time, would not be a suitable surgical risk. Operation dare not be decided upon unless the patient can be brought into a much better state than he now is. Naturally, we should have preferred to have had the opportunity of considering splenectomy before the liver was so markedly enlarged, before these hemorrhages had taken place, and before ascites had developed. However, in a few cases of Banti's disease in which cirrhosis of the liver, with ascites, had already developed, much benefit was still derived from splenectomy. We cannot make a decision with regard to this point at the present time, but must wait for a little period during which the patient will be kept under close observation. I may say, now, however, that I am very doubtful if splenectomy will ever be advisable in this patient for, as a rule, an aplastic bone marrow and thrombosis of the portal system of veins are both contraindications of splenectomy.

In connection with diseases of the blood, let me call your attention to this little book, by Dr. Paul W. Clough, which has just appeared, en-

titled, "Diseases of the Blood." It is a volume that merits a place in the library of every medical student and of every general practitioner. I can also recommend most heartily the little volume on diseases of the blood and blood-building organs by Lucas and Washburn. I wish it could be purchased separately from the rest of the set of treatises in which it is included. Of the larger treatises on diseases of the blood, I can recommend strongly this volume by O. Naegeli, entitled, "Blutkrankheiten und Blutdiagnostik." You will also find much valuable information in this volume by Eppinger, entitled, "Die hepato-lienalen Erkrankungen." But, you will say, these last two volumes are printed in German. Yes, that is true; but nowadays every medical student is supposed to know how to read both French and German. If you do not read these languages easily, I should advise you to read some French and some German every day. I can remember that when I first learned to read medical German I sometimes spent a whole evening translating a single paragraph; but by keeping at it, facility can be gained. Of course, a period of postgraduate study in France and in Germany is of great help in acquiring the medical vocabularies. Medicine is, today, an international subject, and anyone who wishes to keep pace with progress must be able to read at least French and German, in addition to English. If he can read Italian and Spanish also, so much the better. It is often a long time before important things in foreign languages are translated into English. Therefore, if one wishes to keep abreast of the times, he must be able to consult the information available in foreign languages.

It is especially desirable to read the new literature upon the diseases that one meets with in patients, for they afford ever new topics of interest. Show me a medical man who has ceased to read, and I will show you one who will not fail to cease to grow.

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ON THE DIFFERENTIATION BETWEEN CHRONIC AMEBIC DYSENTERY AND CHRONIC NONAMEBIC COLITIS; COMMENTS UPON THE TREATMENT OF CHRONIC COLITIS[1]

THE malady from which the patient before you suffers has presented certain difficulties in diagnosis and Drs. Callander and Rhodes, who have supervised the studies made, have asked me to comment upon the case.

CASE HISTORY

A. M., an Italian woman, age twenty-five years, housewife, has been ill for two and a half years, her chief *complaints* being: (1) frequent bowel movements with mucus and blood in the stools; (2) cramplike pains in the abdomen, and (3) loss of weight and strength.

Present Illness.—Until the onset of this illness, except for a tonsillectomy at twenty, she had always been healthy and of good habits. One day, without apparent cause, she noticed bright red blood in a stool. A few days later, mucus and pus also appeared in the stools, and she began to have great frequency of bowel movements, as many as 20 or 30 each day. Soon she began to experience cramplike pains in the lower abdomen, chiefly on the left side. These symptoms have persisted in variable intensity ever since. During the illness menstruation has been painful, though earlier it was quite normal.

At the end of six months the patient had become extremely ill; she grew so weak that she was obliged to remain in bed; during the period her weight had rapidly decreased from 118 to 74 pounds.

In the two years that have since elapsed, she has remained very ill, though there has been a little improvement; she admits that she is somewhat stronger and her weight has gradually increased though she still weighs only 85 pounds.

During the first eighteen months of her illness, she spent much of her time in hospitals, having received treatment in six different institutions in New York City. In four of the hospitals, the treatment consisted of colonic irrigations, but they relieved the symptoms only temporarily. In a fifth hospital, an operation was performed, probably a cecostomy, following which a tube was left in the right lower quadrant of the abdomen for six months, through which the colon was irrigated regularly. Finally, this tube was removed and her symptoms reappeared and were about as severe as before this radical treatment was instituted. During the two and a half years of her illness, she has had four transfusions of blood.

Family History.—Her father, mother, three brothers, and three sisters are all living and well. She married at twenty-two; her husband is living and well and she has one healthy child, twenty-one months old; there have been no other pregnancies.

Physical Examination.—Small in stature; profoundly undernourished; lips and mucous membranes very pale. Heart and lungs negative.

Operative scar in lower right abdomen. On palpation of the abdomen, there is tenderness over the descending colon and this and the sigmoid are palpable as a firm cordlike mass; abdominal examination otherwise negative.

Marked clubbing of fingers and toes, with longitudinal curving of the nails.

[1] Clinic at the Semi-Annual Meeting of the Alumni of the University of California Medical College, at the San Francisco Hospital, November 22, 1929.

On sigmoidoscopical examination, blood could be seen flowing down from the upper sigmoid. The lumen of the bowel looked tubular, of a grayish color and scarred; only a few areas of normal looking reddish mucosa could be seen. No areas of granulation tissue nor any ulcers were seen. About 9 inches from the anal margin the passage of the sigmoidoscope was obstructed, apparently by a constriction, though the mucosa there could not be said to look abnormal.

x-Ray Examinations (November 13, 1929).—The chest was negative. There was no delay in the passage of barium through the esophagus. The stomach was normal in position, tone, and peristalsis. A small concave deformity was visible on the superior margin of the duodenal cap. The six-hour meal was in the terminal ileum and the cecum.

On November 15, 1929, after a barium enema, the descending colon looked tubular; there seemed to be a constriction about 1 cm. in length where the twenty-four-hour residue had stopped; there was no tenderness on pressure over this spot and the colon at the same site was freely movable. It was feared that the stricture might indicate malignancy though smoothness of its edges was against this view, and it was thought that spasm might account for the condition.

On November 20, 1929, the barium enema was repeated. The colon was then found to be normal in outline; no sign of the constriction observed before could be made out.

Laboratory Examinations.—*Blood.*—Red blood cells, 3,120,000; hemoglobin, 58 per cent; white blood cells, 6680. Differential count: Polymorphonuclear neutrophil leukocytes, 55 per cent; small mononuclears, 34 per cent; eosinophils, 5 per cent; basophils, 1 per cent; transitionals, 5 per cent. The stained smear showed anisocytosis and poikilocytosis. Wassermann negative.

Urine.—Negative.

Smear from Urethra and Cervix Uteri.—Negative for gonococci.

Feces.—Watery, yellowish, with blood-tinged strings of mucus, many pus cells and red blood corpuscles. Many gram-negative bacilli and gram-positive cocci. Many microscopical examinations of fresh stools were negative for parasites and ova. Very careful search on numerous occasions revealed no ameba, no cysts, and no precystic small forms.

Course in the Hospital.—The patient has been afebrile. She averages from three to four bowel movements during the day and from ten to fifteen during the night. Her appetite is good; she eats well of a high-caloric nonresidual diet. She believes that she is improving and is gaining in strength.

DIAGNOSTIC DISCUSSION

This dysentery-like syndrome has persisted for two and a half years, despite prolonged hospital treatment, including months of colonic irrigations administered per rectum, and some six months of irrigation through a cecostomy opening. It has been accompanied by great loss of weight and strength, severe abdominal pain, and a marked secondary anemia. Have we had here to deal with an amebic dysentery, a bacillary dysentery, an intestinal tuberculosis, a chronic ulcerative colitis, a neoplasm of the colon, or only a spastic colon with mucous colopathy? From the standpoints both of prognosis and of therapy, it is important, if possible, to arrive at the correct diagnosis.

Bacillary dysentery (**chronic form**) seems to have been ruled out by bacteriological studies of the feces. By making cultures from washed mucus on litmus-lactose agar and on litmus-mannite agar, followed by

agglutination tests, it is usually easy to discover the *Bacillus dysenteriae* if present and to determine its type.

Amebic dysentery, too, seems to have been ruled out. This disease, in its more chronic forms, is certainly often overlooked; one should always think of the possibility of its existence when a diarrhea persists, especially when blood, mucus, and pus cells are present in the stools. Sometimes the larger vegetative forms of the parasite are absent when cysts or precystic small forms can be demonstrated in the stools. Here on the Pacific Coast you are very familiar with obscure forms of amebiasis and you have the reputation of rarely overlooking them when they exist. The very careful studies of the stools in the laboratories of this hospital have failed to reveal the parasite in any of its forms. I understand, too, that Dr. Kofoid has examined several specimens and could not find any evidence of amebic infection.

The eosinophilia is rather suggestive of some animal parasitism or of protozoan infection, but the stools have contained no flagellates, no *Balantidium coli*, and no *Lamblia*, or *Giardia*. It is possible, of course, that the eosinophilia could be a concomitant of the spastic colon, which undoubtedly exists.

If there were still any doubt regarding the existence of amebiasis, one might make tests by Craig's method, or one might try the therapeutical test of giving one or two courses of yatren pills. I feel confident, however, that the studies already made rule out amebic invasion.

The suspicion of **carcinoma of the colon,** especially of the sigmoid, is always aroused when symptoms like those of the patient are long persistent without other apparent cause, particularly when there is marked emaciation and a severe accompanying anemia. Though the age of the patient militates against the diagnosis, still carcinoma occasionally occurs in young persons. It seems to me, however, that the *x*-ray films after the last barium enema definitely rule out carcinoma.

Diverticulosis of the colon, and **diverticulitis** and **polyposis** have also been ruled out by the roentgenological tests.

The possibility of **tuberculous ulceration** should not be lost sight of, especially when we remember the patient's age. Repeated examinations of the stools have, however, failed to demonstrate the presence of tubercle bacilli, and there is no evidence of tuberculosis elsewhere in the body of the patient.

The symptoms of the patient are not compatible with the diagnosis of **sprue** for the stools have not been bulky, putty colored, or frothy, and there have been no signs of sprue in the mouth.

Syphilis of the intestine would seem to be ruled out by the negative serological reactions.

There may have been a **chronic ulcerative colitis** of bacterial origin, but the roentgenological findings at present and the absence of any visible ulcers on sigmoidoscopical examination would indicate that, if

ulcers have been present, they have healed. There has been much discussion regarding the bacteriological diagnosis of chronic ulcerative colitis. Bargen, of the Mayo Clinic, is decidedly of the opinion that the etiology of the malady has been solved and maintains that if his technic be followed precisely, others must confirm his findings.

Rarer conditions like **Hodgkin's disease, lymphosarcoma,** and **leukemia intestinalis** should be thought of, but the findings in the blood and on physical examination of the spleen and lymph glands make these possibilities seem very improbable.

The malady seems to have been too severe to have been only a **spastic colon with mucous colopathy,** certain as it is that the descending colon is spastic and that there has been marked increase of mucous secretion. That there has been and that there still exists a true inflammatory condition (*colitis*) in addition to the nervous malady of spasm and perverted secretion is made certain, I think, by the constant presence of many pus cells in the stools.

FURTHER TREATMENT OF THE PATIENT

As to the further treatment, I would suggest a continuance of general upbuilding measures. Though the colon should be protected from too irritating a diet, I should try, from now on, forced feeding, and I should be inclined to try to widen the diet so as gradually to return to a well-balanced ration, including an abundance of vitamines. It is exceedingly important that this patient gain 20 or 30 pounds in weight as speedily as possible and that the anemia be overcome. I think that if she were given 8 units of insulin by hypodermic injection, just before the principal meal, weight would more quickly be put on.

The patient should remain in bed until a good part of the weight has been gained. Milk and milk products, including acidophilous milk could be given freely and the bulk of the feces should be increased by non-irritating materials. Agar could be added and even finely powdered bran, I think, without harm. The spasm of the colon can best be overcome by novatropin tablets, or by tincture of belladonna and tincture of hyoscyamus. Since the majority of the stools are passed at night, it might be well to introduce into the rectum at 9 P. M. a suppository containing $\frac{1}{2}$ mg. atropine sulphate, 1 decigram of menthol, 1 decigram of tumenol, and 2 decigrams of bismuth subgallate, using coco butter as a base.

The anemia could be combated by injections of cacodylate of soda or by the administration of elarson tablets by mouth, though improvement of the general nutrition of the patient will be even more important for the restoration of the blood. One or two transfusions of blood might be helpful.

Sleep, now so much interfered with by the frequent stools at night, might temporarily be promoted by the judicious use of barbital.

I see no report upon the stomach contents. If there should be no free HCl present, it would be helpful to give a teaspoonful of the dilute acid with aerated water with each meal.

We shall all watch with interest the further progress of this patient. I am very hopeful that, under the régime above outlined, she may, in time, make a satisfactory recovery. The reports of Bargen on ulcerative colitis should be carefully studied and should the case prove to be rebellious to treatment it would be interesting to test the effects of the therapy that Bargen recommends.

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POLYPOSIS OF THE COLON; DISCUSSION OF THE HEREDOFAMILIAL OCCURRENCE OF THE DISEASE AND OF THE EXTRAORDINARILY FAVORABLE EFFECTS OBTAINED IN ONE CASE BY DEEP *x*-RAY THERAPY[1]

THE subject of intestinal polyposis is one of increasing interest. Though polyposis of the colon was recorded as early as 1724 (two hundred and five years ago) and occasional cases were reported in the earlier part of the last century, it is only in the present century that the prevalence of the disease has become generally recognized. In 1907 some 52 cases were reported from the literature by Doering to which he added two of his own; since then increasing numbers of cases are being recorded in the literature.

The principal reason for the failure of recognition in the past lies in the fact that the clinical picture may long be very vague. Many patients harboring intestinal polyps may go for years without any symptoms, except for occasional diarrhea.

That the disease could occur in families has been known for over thirty years; but the heredofamilial incidence has been strongly emphasized recently by Hüchtemann in a special article on the subject. It is now becoming clear that if a single case of intestinal polyposis appear in a family, all members of the family should be examined with especial reference to the existence of the disease. Very often several members of such a family were devoid of symptoms, though on thorough examination they could be shown to harbor polyps. The careful geneological studies that have been made indicate that the mode of inheritance is by mendelian dominance, for, in several families, cases have been shown to exist in each of three or four successive generations. In one large family it was demonstrated that more than half the children had the disease.

Intestinal polyposis seems to be somewhat more prevalent in women than in men, perhaps in the relation of seven to three or of six to four.

CLINICAL PICTURE OF INTESTINAL POLYPOSIS

As I have said, many patients with polyps in the intestines show no symptoms whatever, whereas other patients suffer from hemorrhages, or from abdominal pain. In some patients there have been recurrent diarrheas.

In the cases reported in the literature the disease was often first recognized on proctoscopical examination. If, therefore, in a family in which 1 case of polyposis has been found to exist, though the other

[1] Amphitheater Clinic at the San Francisco Hospital, December 10, 1929.

members are said to be healthy, one should not take it for granted that they do not have polyps, but should make a complete examination including a proctoscopical examination and an *x*-ray examination (gastro-intestinal series; barium enema).

The *site of predilection* of intestinal polyps is the large intestine, with increasing frequency of polyp formation in most cases as the rectum is approached. There are some patients who have polyps in the stomach and polyps in the large intestine as well. It is probable that most patients with gastric polyposis also suffer from intestinal polyposis. A remarkable feature of the disease is the relative freedom of the small intestines from polyp formation. In one autopsy reported by Wechstellman on a man who died of generalized polyposis, there was one polyp in the stomach, one in the duodenum, three in the jejunum, and one hundred and forty in the colon.

An interesting feature on proctoscopical examination is the finding of a constant alteration of the rectal mucous membrane; it looks reddened and somewhat granular and the vascular markings are indistinct. Jüngling asserts that if one is familiar with the characteristic appearance of the inflamed mucosa in these cases he can prophesy, with fair certainty, from a glance at the mucosa of the ampulla of the rectum, whether or not polyps will be found higher up, even if no clinical symptoms are complained of.

THE GASTRO-INTESTINAL TRACT AT AUTOPSY IN CASES OF POLYPOSIS

When polyposis of the stomach or intestines exists one sees, at autopsy, polyps of two sorts: (1) Those that are pedunculated, and (2) those that are sessile, the latter sometimes forming ridges or flat plates upon the surface of the stomach or of the intestine. The polyps vary markedly in size from that of a pea to that of a hazel nut, a walnut, a pigeon egg, or even larger. In one case, a polyp the size of a child's head was observed!

In polyposis of the stomach the tumors are particularly numerous in the pyloric region, but they may be scattered over the whole wall of the stomach. It is rare that a solitary polyp is found.

Careful histologic studies indicate that there is, first, a proliferative inflammation of the mucous membrane, but, later, adenoma formation occurs and, unfortunately, in a large number of cases, carcinoma finally develops.

Some look upon polyps as merely hyperplastic changes in the mucous membrane, but Konjetzny has shown, I think, conclusively, that we have to deal with true adenoma, for the changes in the mucous membrane are too irregular and the gland proliferation too atypical to be accounted for by simple hyperplasia. We have to deal, therefore, with true neoplasms, adenomata, which may be sessile, wartlike, ridgelike, or polypoid.

ETIOLOGY OF GASTRO-INTESTINAL POLYPOSIS

The cause of polyposis has been much disputed. There is conflict between those who accept the Cohnheim-Ribbert idea that all neoplasms are of congenital origin due to misplaced embryonic rudiments and those who believe that neoplasms may arise upon a basis of chronic inflammation through mechanical or chemical stimuli. The evidence at present favors the latter view. Those who favor the embryonic view base their argument upon the outspoken heredofamilial disposition and upon the fact that the disease may appear in early youth. But disposition alone will scarcely suffice to explain the origin of the disease; there must also be releasing factors that are operative. Undoubtedly, a constitutional factor is concerned, for otherwise a heredofamilial history would not be so common. The releasing factors seem to consist of local irritations. The view that accords best with the known facts is that which assumes an inherited disposition to pathologic response to irritation combined with long-continued irritation from the mechanical and chemical irritants that pass through the gastro-intestinal tract. It looks as though persons who are constitutionally predisposed to the disease cannot bear even the natural stimuli of the food residues that pass through the gastro-intestinal canal without responding in a pathologic way; first, gastro-enteritis develops, later there is proliferative inflammation, then adenoma formation, and, finally, carcinomatous development.

RELATION OF POLYPOSIS TO CARCINOMA

All who are familiar with the disease now recognize that gastric and intestinal polyposis are precancerous diseases. It is possible that carcinoma of the stomach and carcinoma of the rectum are much more frequently preceded by adenoma formation than was previously supposed. Schmieden believes that most cases of rectal carcinoma arise from polyps. Still, one must admit that, in ordinary cases of carcinoma, there is no evidence of mendelian dominance, whereas, in the carcinomas that develop upon a polypoid basis, mendelian dominance is often very striking in the family history.

It is true the prognosis of polyposis of the rectum has had to be very guarded because of the frequency of the development of carcinoma. In the family described by Jüngling, all members in the first generation who had polyps died of carcinoma of the rectum; in the second generation, of 8 cases of polyposis, one has died of carcinoma of the rectum and of tuberculosis of the intestine; and, in the third generation, one patient died from hemorrhage, and two who are still living are as yet free from carcinoma.

Treatment of gastric and intestinal polyposis has hitherto been most unsatisfactory. Irrigation has been tried, with and without colostomy; and wide resections have been done. Recently, another method of treatment

has been introduced, which promises more; I shall speak of it later on during the hour.

Thanks to the courtesy of Dr. Alson R. Kilgore, I am fortunate to be able to present to you today the histories of 2 cases of gastro-intestinal polyposis. One of the patients died and I can show you the specimens obtained at autopsy. The other patient is living and is before you; he has made a remarkable recovery under a treatment to be described presently.

Case I.—The patient, Everett H. J., a white brakeman, age twenty-four years, was admitted to the San Francisco Hospital on October 23, 1928 where he died the next day of bronchopneumonia.

He had, earlier in his life, complained of no symptoms referable to the gastro-intestinal tract. Three weeks before admission, he developed a cough, headache,

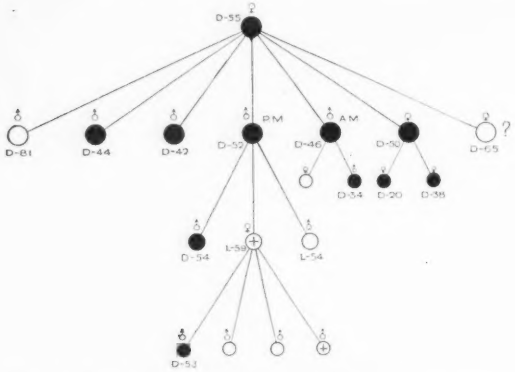

Fig. 5.—Family tree of the patient, Everett H. J. (see text).

malaise, and a little fever, associated with abdominal cramps, diarrhea, and weakness of three days' duration.

On physical examination, there were signs of an influenzal infection in the lungs with a possible bronchopneumonia because of fine râles audible at the left base. The abdomen was tympanitic and was slightly tender on deep palpation. Dr. Kilgore's assistant, Dr. Foree, having heard that other members of the family had exhibited polyposis, made a rectal examination and found an irregularity of the mucous membrane that suggested the presence of polyps.

After death, extensive polyposis of the rectum and of the descending colon (Fig. 5) was found in addition to the terminal bronchopneumonia.

The family tree of this patient is very interesting, inasmuch as it shows clearly a mendelian dominance; the black circles represent cases of polyposis (Fig. 5).

In the third generation, the middle individual is our patient's mother, operated upon eighteen years ago by Dr. Rixford for carcinoma in polyposis of the descending colon and within the past year operated upon again for palliation (short-circuiting) of a carcinoma of the hepatic flexure, at the University Hospital. No further polyposis was described at the last operation. All individuals shown in black died of carcinoma

of the bowel. The last individual in the fourth generation is our patient, who had polyposis but died of intercurrent disease. The accompanying photograph of a por-

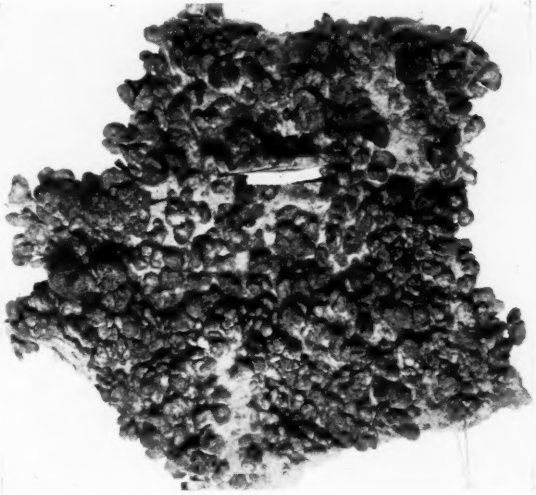

Fig. 6.—Photograph of a portion of the colon of the patient, Everett H. J., showing the great number of the polyps.

tion of the colon shows the lesions well (Fig. 6). The actual specimens are in the jars before you.

Case II.—The second patient, E. G., age sixty-three years, a graduate in medicine, now a railway station master, was studied by Drs. Seldman and Jelte and also by Drs. Alson Kilgore and Rehmrich.

He was first seen on March 24, 1929, when he gave a history of intermittent diarrhea without blood and without pain, for the previous six months. He had lost about 20 pounds in weight and had become very weak.

On physical examination, there were multiple hard, irregular masses palpable in the abdomen, chiefly on the right side in both the upper and the lower quadrants, but extending down also into the right lower quadrant. These masses were hard, and they were apparently not fixed, either to the abdominal wall or to the deeper structures. The impression given on palpation was somewhat similar to that obtained in cases of carcinomatous infiltration of the omentum.

The patient entered a hospital in Los Angeles for a proctoscopical examination, which was reported as negative; but, on *x*-ray examination, a report was made of "diffuse hyperplasia of the mucous membrane of the transverse and descending colon."

This man returned to San Francisco about May 1st and, during the next two months, became progressively worse, though without much increase in the size of the palpable masses. He continued to lose weight, to become weaker, and to have persistent diarrhea.

On *x*-ray examination here, a remarkable picture was seen (Fig. 7). There was a most extensive honeycomb-like appearance of the cecum, ascending colon, transverse colon, and upper part of the descending colon. The *x*-ray findings were characteristic of extensive polyposis of the colon, involving the parts mentioned.

An interesting experiment in treatment was then undertaken. On September 1st he was given, by Dr. J. Rehfisch, a course of deep *x*-ray therapy, at 200,000 kv., 70 cm. distance, 35 cm. port., aluminum 1 mm.,

Fig. 7.—Roentgenogram of the colon after barium enema had been given to the patient, Edgar G. The honeycomb-like appearance of the cecum, ascending colon, and proximal transverse colon is well shown. There is also evidence of some polyposis of the descending colon.

copper $\frac{1}{2}$ mm. On August 8th to 9th, he was given 270 ma., front and back. On October 21st to 25th he was given 270 ma., front and back.

Shortly after the first *x*-ray treatment, he reported passing numerous small macerated grapelike masses. On section of one of these masses, it showed only necrotic tissue, but in its formation the connective-tissue framework was like that of a polyp.

Coincident with the passing of these masses, the general condition of the patient showed a rapid and very marked improvement.

At the examination made on September 26, 1929 all that could be

felt remaining of the abdominal masses were small ones, deep in the lower left quadrant. The diarrhea had ceased. The patient had gained in weight from 142 to 156 pounds and he showed corresponding improvement in strength. He became able to return to his ordinary work in October.

Roentgenograms were taken on September 27, 1929 and showed a very marked retrogression of the polypoid condition (Fig. 8). There were, however, still a few areas of irregular outline visible, suggesting the persistence of a few of the polyps.

Fig. 8.—Roentgenogram of colon of Edgar G., showing the remarkable effects of deep roentgenotherapy upon the polyposis. (Compare this figure with Fig. 7.)

The changes brought about in this patient by *x*-ray therapy are among the most remarkable that I have ever had the opportunity to observe. Here you have the indubitable evidence, through comparison of roentgenograms, of the extraordinary effects of deep *x*-ray therapy upon colonic polyposis. It is possible that this patient will have to have still further deep *x*-ray therapy in order to remove the remaining polyps.

It will be interesting to find out whether or not this form of therapy will similarly benefit other cases of gastro-intestinal polyposis. If we can remove intestinal polyps by this simple method, we shall have made a very great advance in the therapy of the disease and perhaps we

shall be able to help patients to escape the tragic fate that hitherto has seemed to await the victims of intestinal polyposis, namely, carcinoma as a final stage of the disease.

I should like to emphasize that the dosage of *x*-ray administered was heavy. I have asked the patient how he bore it and he states emphatically that it was "a very trying ordeal," and that he was very sick, temporarily, after the treatment. Still, he is naturally glad that he went through it because of the results that have been obtained. How permanent the benefit will be still remains to be seen; the further progress of the case will be watched with the deepest interest.

I think that you are to be congratulated upon the large amount of good work that has been done upon polyposis of the stomach and of the intestine here on the Pacific Coast. Local interest in the disease seems to have been excited by the paper on gastric polyposis published by E. S. DuBray in 1920. In the same year, I find a paper by Dr. H. E. Ruggles on the *x*-ray findings in polyposis. I understand that in Portland, Oregon, Dr. Coffey and others have been deeply interested in the disease. On the topic I find a paper by Drs. Brunn and Pearl, published in 1926, one by Chapman, of Pasadena, in 1928, and in 1929 one by W. W. Washburn. In Washburn's case there were multiple polypi in the jejunum, one of them causing intussusception. Now you have added to these other studies these interesting experiments with the *x*-ray as a therapeutical agent in this remarkable disease.

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THREE CASES OF PORTAL CIRRHOSIS OF THE LIVER WITH COMMENTS ON ETIOLOGY, ON SOME OF THE NEWER TESTS OF HEPATIC FUNCTION, AND ON THERAPY[1]

I AM among those old-fashioned medical educators who still believe in the value of the amphitheater clinic.

As you know, the modern trend has been away from the formal clinic. It has been urged that the only clinical education worth while for the medical student is that which he gives himself by actually talking to and examining patients, under the guidance of experienced men, at first, and, later, by self-guidance. It has also been maintained that the student can always acquire by himself from a library all that the clinic giver can tell him of mere facts.

Though no one values more highly than I do the direct relationship of student with patient as a means of education, or the importance of self-education by the reading of selected books and articles obtainable in libraries, I still maintain that the well-conducted amphitheater clinic has its place and an important place in the development of medical youth. Note that I say "well-conducted," for, otherwise, the tediousness of a pedantic didacticism may be more harmful than useful. But properly coordinated with the practical-technical training in the wards, out-patient departments, and clinical laboratories, teaching by means of the amphitheater clinic can be most useful not only to the giver of the clinic, but also to the student hearer. A gifted clinician can stimulate and inspire by this method in a manner unapproachable by other methods of teaching. Interest can be excited, diligence and enthusiasm can be spurred, clinical problems can be formulated, the best methods of solving them can be demonstrated, clinical reasoning can be illustrated, and clinical judgment can be exemplified in a manner most helpful to the growing mind. No text-book can take the place of the living personality of the teacher. Even sheer information can be imparted in a lively and purposeful way that may be incomparably more profitable than that obtainable in libraries.

The three patients that have been selected for the clinic today have been carefully studied by the medical staff, Drs. Kerr, Briggs, Hein, Bruck, Shepardson, and their associates. They illustrate well one of the commoner forms of disease of the liver and they give me the opportunity of discussing, not only the symptomatology in each of the three cases, but

[1] Clinic at the San Francisco Hospital before the Alumni of the University of California Medical School, Friday, November 22, 1929.

also the conceptions that are current regarding etiology and some of the functional tests that are of value in estimating the degree of impairment of working capacity of the principal organ concerned.

CASE I

The first patient, Patrick R., a white manual laborer, age sixty-two years, was admitted to the San Francisco Hospital, November 6, 1929.

His *complaints* were of dull aching pain in the upper part of the abdomen, distention of the abdomen, and aching in the joints (elbows, knees, and shoulders).

The **present illness** must have begun a long time ago, but the patient himself ascribes the onset to the time when he first noticed the symptoms of which he complains, about two months prior to admission. The pains in the abdomen were not severe and were referred to the midregion of the upper abdomen and the right side of the midabdomen rather than to the right upper quadrant. The discomforts in the joints were also mild; he describes them as "aches" rather than as "pains." About a week after the onset of the abdominal pain, he noticed swelling of the abdomen, which persisted and had increased up to the time of his entrance to the hospital.

The **family history** throws no light upon the case.

In the patient's **past history,** it is stated that he had gonorrhea at seventeen (without complications and with quick recovery), and that at fifty-one he suffered from influenza (during the epidemic of 1918), which kept him in bed for a month.

Except for an accident to his right foot some twenty-five years ago he has suffered no traumata, and he has had no surgical operations. Indeed, except for a tendency to constipation and the two infections mentioned, he seems to have been an unusually healthy man.

He admits having been a moderate drinker during most of his life, but the alcohol was taken chiefly in the form of wines and beer, as he did not care for whisky, gin or other forms of "hard liquor." He has been a liberal eater and was for a long time somewhat obese, averaging 195 pounds in weight (maximal weight 215 pounds), but during the past two months he has lost weight rapidly so that at present he weighs only 167 pounds.

On **physical examination** here, he was found to be well developed and well nourished (despite the recent loss in weight) and of strong musculature. The lips and mucous membranes were of good color, except that there was a subicteric tint to the sclerae. There was slight edema of the feet and legs, which pitted on pressure. A number of small angiomata were visible over the chest, and the veins over the midabdomen and lower chest were dilated (beginning collateral circulation from the portal to the caval system). He had lost all his teeth but two, though otherwise the mouth and the pharynx were negative. The temperature, pulse rate, and respiratory rate were normal. There was no enlargement of the lymph glands.

The thorax was somewhat emphysematous in type. Examination of the lungs was negative except for a few moist râles at the bases. There was slight enlargement of the heart, and a loud systolic murmur was audible at the apex and over the body of the heart, maximal over the fourth costal cartilage near the left margin of the sternum. The peripheral arteries were definitely thickened; the blood pressure was 112 systolic, 60 diastolic.

On examination of the abdomen, there was marked diastasis of the recti, very noticeable in the upper abdomen when the patient sat up. On palpation the liver was enlarged, reaching a hand's breadth below the costal margin in the right mammillary line; the edge was thin and the consistence of the liver was markedly hard. Ascites was easily demonstrable on palpation and on percussion. On admission, the spleen could not be felt, but after paracentesis the lower end of the spleen became palpable.

On rectal examination, some external hemorrhoids were found and the prostate

was enlarged and firm, though it was not nodular and there were no obstructive symptoms. Neurological examinations were negative.

On **laboratory examination** the findings were as follows:

Blood.—Red blood cells, 4,800,000; hemoglobin, 98 per cent; white blood cells, 7800; differential count normal. Wassermann negative. Icteric index 15. Qualitative van den Bergh, biphasic, direct; quantitative, 7.5 mg. of bilirubin per liter of blood (1½ units).

Stool.—Negative for blood, parasites and ova.

Ascitic Fluid.—Specific gravity 1.013; cell count 450 (endothelial cells chiefly, with a few polymorphonuclear leukocytes); fluid straw colored; direct smear negative for bacteria; culture negative; Wassermann negative; Rivalta test negative.

Urine contained a trace of albumin, a few hyaline casts, a few white corpuscles, some bile and some urobilin.

Rose bengal test of liver function showed marked impairment of the power of the liver to excrete the dye.

Diagnosis.—1. *Cirrhosis hepatis* (with enlargement of the liver and spleen, portal obstruction, hemorrhoids, constipation, ascites, and slight edema of the lower extremities).

2. *Arteriosclerosis of decrescent type* (with thickening of peripheral arteries, low blood pressure, systolic heart murmur, and mild renal changes).

3. *Chronic alcoholism* (moderate).

4. *Slight arthropathy* (with aching elbows, shoulders, and knees).

5. *Benign prostatic hypertrophy.*

CASE II

The second patient, Thomas S., a single white laborer, age sixty-seven years, entered the San Francisco Hospital for the third time on October 18, 1929, with the *complaint* of swelling of the abdomen for three months, during which period he had been tapped six times with withdrawal of large amounts of fluid.

He had been first admitted to the hospital in 1920; at that time the diagnosis of cerebrospinal lues and of estivo-autumnal malaria was made. On a second admission in 1922, he was found to be suffering from chronic hypertrophic arthritis and he complained of a pain in the right upper abdominal quadrant, the nature of which could not at the time be determined.

His **previous history** indicated further that he had used whisky and beer "in moderation" for many years. Other than this and the illnesses studied during the two previous hospital sojourns, the past history was negative.

On **physical examinations** made by the hospital staff the chief positive findings consisted of the following: Marked emaciation; outspoken pallor of skin and mucous membranes; faulty oral hygiene; thickened peripheral arteries; low blood pressure (90 systolic, 60 diastolic); marked abdominal distention with evidence of free fluid in the abdominal cavity; diastasis of recti muscles; large reducible umbilical hernia; enlarged, rough, hard liver (edge palpable three fingerbreadths below tip of xiphoid); enlarged palpable spleen; fixation of lower thoracic and lumbar spine.

Laboratory Tests.—*Blood.*—Red blood cells, 3,750,000; hemoglobin, 50 per cent; white blood cells, 7400; differential count showed polymorphonuclear neutrophil leukocytes, 80 per cent; Wassermann negative; blood urea 43 mg. per 100 cc.; icteric index 20; van den Bergh test, direct, immediately positive; quantitative, 10 mg. of bilirubin per liter (2 units). Blood sugar 85 mg. per 100 cc.

Urine.—Negative except for the presence of urobilin. Phthalein output reduced to 25 per cent in two hours.

Sputum.—Negative.

Cerebrospinal Fluid.—Cell count 6 (small mononuclears); globulin negative Wassermann negative; colloidal tests negative.

Ascitic Fluid.—Transudate rather than exudate; bacteriological and serological tests negative.

Rose Bengal Test.—Marked retention of dye in blood at end of eight and of fourteen minutes.

Diagnosis.—1. *Cirrhosis hepatis* (with portal obstruction; ascites, umbilical hernia, latent jaundice, and history of pain in right upper quadrant).

2. *Generalized arteriosclerosis of decrescent type* (with low blood pressure 90/60 and some impairment of renal function).

3. *Moderate chronic alcoholism* (wines; beer) and history of earlier luetic and malarial infections.

4. *Undernutrition and cachexia.*

5. *Marked secondary anemia* (red blood cells, 3,750,000; hemoglobin 50 per cent).

6. *Chronic hypertrophic arthritis* (of joints of thoracic and lumbar spine).

7. *Faulty hygiene.*

CASE III

The third patient, Oscar P., a white laborer, forty-nine years of age, was admitted to this hospital November 12, 1929.

Complaints.—Yellow color of skin and itching; swelling of the abdomen; passage of blood by the bowel; cough and spitting of blood; rupture.

Onset of Present Illness.—About four months ago, the patient noticed that his feet were occasionally slightly swollen, but the swelling was transient. Some two months ago, in a paroxysm of coughing, he developed a right indirect inguinal hernia (reducible). With coughing there has been some spitting of blood (on one occasion about half a cupful). Recently, there has been some bright red blood in the stools. Ten days before admission he noticed that his abdomen was swollen, that his skin and the whites of his eyes were yelllow, that there was marked itching of the skin, and that he felt pain in the abdomen, which radiated to the right shoulder. His symptoms grew progressively worse and led him to apply to the hospital for diagnosis and treatment.

In the **past history** it is recorded that he had yellow fever at the age of twenty-four (when in Brazil), that he had pneumonia at thirty-five, and that, at thirty-nine, a right-sided bubo was incised, after which he took mercury and arsenic for one year.

His **habits** have been intemperate as regards food and alcohol. He was obese, weighing 200 pounds one year ago, though recently he has lost weight and now weighs only 174 pounds. He has been a heavy drinker, taking a quart of whisky daily over considerable periods. Such periods alternated with periods of abstinence. During the month before admission he had been drinking steadily and heavily.

On **physical examination,** the temperature, pulse rate, and respiratory rate were normal. The patient, despite his loss of weight, was still moderately obese. He seemed apathetic and depressed, and he looked older than his stated age. The eyes were watery and the venules of the nose and cheeks were prominent (hepatic facies). He was moderately jaundiced and the skin showed numerous excoriations due to scratching because of pruritus. A collateral venous circulation was evident over the abdomen and lower chest (early caput Medusae). The current in these veins flowed from below upward. There were numerous "spider nevi" over the upper chest. The venules over the shins were dilated and the skin there pigmented. The lymph glands were not enlarged except in the axillae where a number of small glands were palpable (more noticeable on the left than on the right side).

There was *fetor ex ore,* faulty mouth hygiene, dry tongue, and evidence of chronic tonsillar infection.

The lower chest wall was somewhat edematous and moist râles were audible at both bases. The heart was not enlarged; there were no heart murmurs. The peripheral arteries were palpably thickened; the blood pressure was 140 systolic, 115 diastolic.

There was much free fluid in the abdomen and a well-marked fluctuation wave.

Liver and spleen were not felt. A right inguinal hernial sac contained fluid. There was a small varicocele on the left side. No hemorrhoids. No enlargement of the prostate.

The knee jerks and the ankle jerks could not be elicited, though the deep reflexes in the upper extremities were active and equal. The pupils reacted to light and on accommodation. There have been some paresthesias in the feet.

On laryngoscopical examination, a small bleeding ulcer was seen on the left vocal cord.

Laboratory Findings.—*Blood.*—Red blood cells, 4,000,000; hemoglobin, 80 per cent; white blood cells, 11,500; normal differential count; Wassermann negative.

Urine.—Negative except for slight urobilinuria.

Feces.—Negative for ova and parasites; no blood in stools now.

Ascitic Fluid.—Six thousand cc. removed by paracentesis; yellowish color; turbid; specific gravity 1.010; cell count 260 (endothelial cells); Rivalta negative; Wassermann negative; culture and smears negative.

Liver Function Tests.—Icteric index 30 to 60; qualitative van den Bergh, immediate, direct positive; quantitative 26 mg. bilirubin per liter (5.2 units); rose bengal test showed impaired total function; modified glucose tolerance test showed impaired carbohydrate function of the liver.

Diagnosis.—1. *Portal cirrhosis of the liver* (with jaundice, pruritus, portal obstruction, ascites, etc.).

2. *Arteriosclerosis* (with thickened peripheral arteries, ringing aortic second sound, but blood pressure only 140 systolic, 115 diastolic).

3. *Chronic alcoholism* (marked).

4. *Chronic tonsillitis.*

5. *Slight anemia* (but with high color index and associated with paresthesias and areflexia; incipient Addison-Biermer anemia and beginning funicular myelopathy to be kept in mind as a possibility, though the abnormal neurological signs are more likely due to a toxic degeneration of the lower sensory neurones because of alcoholism).

6. *Right inguinal hernia* (indirect).

7. *Obesity.*

8. *Varicocele* (left).

9. *Hypothymic mood.*

10. *Ulceration of left vocal cord* (with history of hemoptysis; possibility of bronchial neoplasm to be kept in mind).*

ETIOLOGY OF PORTAL CIRRHOSIS OF THE LIVER

We can feel fairly confident, I think, that in these three patients we must have dealt with ordinary portal cirrhosis of the liver (the so-called "atrophic cirrhosis" of Laënnec), since the criteria for the diagnosis of the other forms of portal cirrhosis (Banti's disease, Mallory's toxic cirrhosis, cirrhosis with hemochromatosis, and cirrhosis with progressive degeneration of the lentiform nucleus) are lacking.

In all three there is a history of chronic alcoholism, most marked in Case III, less marked in Case I and Case II. In Case II the poisons of lues and malaria may have been of importance; in Case III, the earlier attack of yellow fever should be borne in mind as a possible etiologic factor.

* This man died on March 21, 1930, and an autopsy was made by Dr. Z. E. Bolin who writes me that he found a sclerosis of the liver, probably following a toxic necrosis, along with splenomegaly, esophageal varices, hemorrhoids, and ascites.

So convinced have physicians been of the importance of alcohol as the principal etiologic agent in Laënnec's cirrhosis that they often refer to it as "alcoholic cirrhosis" or "gin-drinker's liver." That the alcohol, itself, especially when taken in drinks of high alcoholic concentration upon an empty stomach, may be the noxa that directly injures the liver cells in the periphery of the liver lobules, seems very probable; there are some, however, who believe that substances in the drink other than alcohol may be just as important as the alcohol itself, and still others who believe that the alcohol acts indirectly by causing catarrhal inflammations of the gastro-intestinal tract and thus setting free toxic substances (like fatty acids or enterogenous toxins) that do the damage to the liver.

It must be admitted, however, that the alcoholic etiology is disputed by some pathologists; certainly, experiments upon the production of cirrhosis in animals by alcohol have not been conclusive. One of my colleagues in Baltimore died of portal cirrhosis of the liver of the Laënnec type; he was a total abstainer. Whatever the noxa, there must have been, in these three patients, degeneration of the liver cells in the periphery of the liver lobules, inflammatory infiltration of the interlobular tissues and, later, new formation of connective tissue with penetration of the lobuli with the same. Along with the degenerative process there is always some regeneration of liver tissue (recognizable at autopsies as groups of large cells with clear protoplasm and nuclei rich in chromatin), and some proliferation of the small bile canaliculi. Differences in the histologic appearance of different livers have led some pathologists to the view that different noxae may be responsible, in other words, that the atrophic cirrhosis of Laënnec may ultimately be resolved into several groups. Certainly the so-called "toxic cirrhosis" of Mallory would appear to represent a malady that is not identical with the atrophic cirrhosis of Laënnec; I hope at another clinic to be able to show to you a typical case of "toxic cirrhosis" and then may comment on its etiology.

THE NEWER TESTS OF LIVER FUNCTION

During the past few decades, physiologists have assiduously studied the functional activities of the liver, and clinicians have made valiant efforts to devise methods of testing both the total function of the liver and its several partial functions. In the article by F. C. Mann in the *Wisconsin Medical Journal* for April, 1929 (which I am passing around) you will find a very good review, from the standpoint of the physiologist, of the present status of our knowledge of the hepatic functions. Though Mann is of the opinion that "the stage has not yet been reached in which much of the newer physiology of the liver can be applied to clinical medicine," still the future possibilities of using such facts in clinical medicine would seem to be great.

The capacity of the liver parenchyma for regeneration is extraordinary; one may, in a dog, remove nearly half of the total volume of the liver

surgically and yet within a few weeks' time, the liver will have regenerated so that the animal has as much liver tissue as before the operation. Our knowledge, today, of the function of the liver in excreting bile, of the glycogenic function and that of maintaining a fairly constant sugar concentration of the blood, of the function of splitting off of nitrogen from amino-acids with formation of urea, of the function of the liver in the metabolism of fats, is much more comprehensive and satisfactory than ever before. Researches, too, upon the relation of the liver-activity to blood-coagulation factors, to mineral metabolism (especially iron metabolism and the storage of copper), to the water balance in the body and the control of water distribution in the body, and to detoxification are in active progress.

In many medical centers in this country, as well as in the medical institutes in Europe, great interest is being evinced in the functions of the liver and in the devising of tests to measure them (see the review by S. Isaac, 1925, and that of H. Staub, 1929). Even in Japan, a number of papers upon this topic have appeared recently, especially upon the excretion of dyes and upon yakriton (detoxicating hormone).

The methods of estimating the impairment of the function of bilirubin excretion (van den Bergh tests and Meulengracht's icteric index) are now so well known and so universally applied that I need only mention them. In Prof. Longcope's clinic in Baltimore interesting studies upon certain partial functions of the liver (protein metabolism function; bilirubin excretion function) are now in progress.

Time will not permit me to discuss the clinical applications of the newer studies in any detail, though I should like to comment upon the methods of estimating total function by dyes and upon a special method of estimating carbohydrate function—methods to the elaboration of which the laboratories and the medical department of the University of California have made, and are now making, notable contributions.

Methods of Estimating the Total Function of the Liver Through Studies of the Elimination of Dyes from the Blood Through the Bile.—For some time it has been known that the liver has the capacity to withdraw certain dyestuffs from the blood and to excrete them through the bile, and this chromogogic function of the liver has been utilized as a test of the "total function" of the organ.

The phenoltetrachlorphthalein test, especially as applied by Rosenthal who estimated the rate of disappearance of the dye from the blood stream after intravenous injection, was for a time the best of these chromodiagnostic tests. Still better was the bromsulphalein test of Rosenthal and White, since this eliminated certain difficulties inherent in the earlier methods of testing employed. Rosenthal certainly deserves great credit for the contributions he has made to the testing of liver functions. But one of the dyes used by Evans, namely, "rose bengal," would seem to fulfil, better than any other yet used, the ideal requirements of

a dye for the study of liver function (as formulated by Delprat), since it is a nontoxic, crystalloid substance, which is eliminated from the body by the cells of the liver parenchyma and yet remains in the circulating blood long enough after injection to permit of determinations of its concentration in the blood plasma. It had been shown by Prof. Carl Schmidt, of your Department of Biochemistry, that dyes of the fluorescein series that contain six or more halogens per molecule are eliminated entirely by way of the bile, whereas those that contain less than six halogens may be eliminated by both the urine and the bile. Rose bengal is a di-iod-tetra-chlor-fluorescein of the triphenylmethane series; it has proved to be very satisfactory for the purpose in mind. Though the technic first employed was rather circumstantial, the recent simplification of the method makes the test easily applicable by anyone accustomed to the methods of the modern clinical laboratory. You will find a full description of the test (as now applied) in the article by Epstein, Delprat, and Kerr, published in the *Journal of the American Medical Association* on May 21, 1927.

In normal persons, only about 50 per cent of the dye remains in the blood at the end of eight minutes and only about 25 per cent at the end of sixteen minutes, whereas in cirrhosis of the liver from 65 to 85 per cent may remain at the end of eight minutes, and from 40 to 75 per cent or more at the end of sixteen minutes.

In all three patients shown here today there was marked retention of the rose bengal dye in the blood. Since in cardiac decompensation, in tuberculous peritonitis, and in peritoneal carcinosis the dye is eliminated almost as in normal persons, the test is obviously of great value in discriminating among conditions associated with the accumulation of fluid in the peritoneal cavity. Acute infections of the liver cause a marked impairment of the capacity of the liver to excrete the dye, whereas that capacity does not appear to be diminished by the nephrotoxemias of pregnancy. We shall watch with interest further studies made with this test here and elsewhere, since it seems probable that the simple technic now employed will soon lead to its widespread use.

Method of Estimating the Partial Function of the Liver in the Regulation of the Blood-sugar Level.—Since coming to your clinic my attention has been called to the method you are now using to determine defective function of the liver in the regulation of the blood-sugar level. When the article by Dr. Althausen and Dr. Kerr upon the results of insulin therapy in the diabetes of hemochromatosis, appeared in *Endocrinology*, in 1927, I was much struck by the peculiar behavior of the sugar in the blood in the patient after the injection of insulin, a behavior that was attributed to a disturbance of the liver function due to the cirrhotic changes in the liver accompanying the hemochromatosis. I am not surprised, therefore, to find that you have been attempting here to make use of glucose and insulin as a test of the function of the liver

that is concerned in the regulation of the blood-sugar level. And I am delighted to have become acquainted with the results of the studies thus far made. If it should turn out, as seems probable, that by this method you can often distinguish between the "toxic cirrhosis" of Mallory and the ordinary atrophic cirrhosis of Laënnec, you will have added another interesting chapter to your clinical studies of hepatic function in disease.

It will be desirable, I think, to find out in how far the results of your modified glucose test parallel those yielded by the *galactose tolerance test* with respect to the regulation of the level of the blood sugar.

Other Tests of Partial Functions of the Liver.—The methods thus far devised for testing the functions of the liver in intermediary metabolism, aside from its carbohydrate-regulating function, are far from satisfactory.

As to the part played by the liver in *protein metabolism*, it may be said that the function of urea formation and that of removal of nitrogen from amino-acids does not seem to be much disturbed until profound changes in the liver have occurred. The determination of the fibrinogen content of the blood is also of but little value as a test of liver function, though it is found to be diminished in about half of the cirrhosis cases. I am very hopeful that the studies now under way in Prof. Longcope's clinic in Baltimore may throw greater light than has yet been gained upon the rôle of the liver in protein metabolism.

Tests for the function of the liver in *fat and lipoid metabolism* have also been introduced, but the interpretation of the results obtained has been difficult. The studies of S. Leites on the metabolism of fats and lipoids promise to throw much light upon this hitherto obscure field. On comparison of the arterial and venous blood of different organs, Leites found that the spleen and the lungs retain lipoids and give off neutral fat or cholesterin. On the contrary, the liver, at a definite phase of fat assimilation, takes up neutral fat and gives off cholesterin, which goes into the blood. It would appear that there is no such thing as an "alimentary exogenous hypercholesterinemia or hyperphosphatidemia," but an increase of the cholesterin or of the phosphatides in the peripheral blood is always due to endogenous lipoids, representing "the resultant of the intermediary lipoid metabolism." Tests that estimate the content of the blood in cholesterin four hours after the administration of olive oil and cholesterin (Burger and Habo) yield results that are not easy to evaluate in terms of liver function.

The test for estimating quantitatively the *relation of free cholesterin to cholesterin esters in the blood* may be clinically more important. In the liver there are both esterifying and ester-splitting ferments. In injury to the parenchyma of the liver, there is often a marked reduction of the esters in the blood (*Estersturz* of Thannhauser and Schaber), or an entire absence of esters. Staub has confirmed these findings in obstructive jaundice and in cirrhosis.

The tests of the *capacity of the liver to excrete bilirubin and the biliary acids* are really valuable as measures of these partial functions of the liver and the technic of these tests is becoming ever more precise. In this connection I would refer you to the interesting studies by G. A. Harrop, Jr., in the medical clinic at the Johns Hopkins Hospital.

TREATMENT OF PORTAL CIRRHOSIS OF THE LIVER

The indications for therapy in these three patients are twofold: (1) The prevention of further damage to the liver, and (2) the relief of symptoms caused by the disease.

To prevent further damage to the liver these patients should abstain from the use of alcohol in any form, and should avoid rich and highly spiced foods. The diet should consist of easily digestible foods, and should be relatively poor in protein, though some milk, eggs, chicken, and fish may be permitted. Easily digestible carbohydrates and fats may be given to supply necessary calories, and, of course, stewed fruits, green vegetables, tomato juice, and orange juice may be given for their vitamine content. Unfortunately, the cirrhosis has already progressed too far in all three of these patients to allow us to expect very much from the institution of prophylactic measures. Such measures are, however, often most beneficial for persons who have been alcoholic but have not yet developed ascites, enlargement of the spleen, or esophageal hemorrhages. If such alcoholic persons begin to be troubled with gastro-intestinal disturbances (meteorism, constipation, hemorrhoids) they should be warned of the probability of a developing cirrhosis hepatis and should be urged to observe the most stringent preventive measures. If the liver has become palpable and of increased consistency, the existence of cirrhosis will be certain and ascites will, in all probability, sooner or later appear.

For the symptomatic relief of the gaseous indigestion and the chronic constipation of cirrhotic patients, we must rely chiefly upon dietetic-hygienic measures. The diet should be suitable, nonirritating, and nonbloating. One may permit one or two pints of milk, boiled or poached eggs, tender vegetables, stewed fruits, and cereals with sugar and cream. When there is much flatulence, despite careful diet, one may give animal charcoal or bolus alba, and one may allow gas to pass by rectal tube. When there is an achlorhydria, dilute hydrochloric acid should be given. In persistent constipation, mineral oil and agar-agar after meals regularly will usually afford sufficient relief.

To relieve pruritus, which is sometimes troublesome, a lotion of 1 per cent thymol or 1 per cent menthol in alcohol may be found to be helpful.

Should ascites appear we may limit the intake of water to 1 quart daily and of common salt to 45 grains daily and we may try to promote diuresis with caffeine sodium salicylate or with theocin. Instead of

water as a drink one may allow, occasionally, a wineglassful of the following solution:

Acid tartrate of potash, ℥j
Juice of half a lemon
One tablespoonful sugar
Boiling water, 1 pint
Stir until cold and strain.

If the ascites persist and increase one must draw off the fluid by paracentesis. This should be repeated as often as is necessary to promote the comfort of the patient. In time a collateral circulation may develop of sufficient grade to overcome the ascites. I remember one private patient who had been tapped over fifty times, after which the ascitic fluid ceased reaccumulating.

Of the operations to prevent fatal hemorrhage from esophageal varices and to promote the development of collateral circulation to overcome the ascites I am to speak in another clinic in this series.

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CIRRHOSIS OF THE LIVER WITH ASCITES, SPLENOMEGALY, SECONDARY ANEMIA, AND ENDOCRINOPATHIES IN A GIRL OF SEVENTEEN: COMMENTS UPON DIFFERENTIAL DIAGNOSIS OF COARSELY NODULAR TOXIC CIRRHOSIS FROM BANTI'S DISEASE AND OTHER CIRRHOSES; TREATMENT OF CIRRHOSIS OF THE LIVER[1]

For almost a year the patient, whose maladies are to be discussed in the clinic today, has been under observation for shorter or longer periods, both in the medical and in the surgical service of this hospital. There are many interesting features, as you will all agree after hearing the summary of the anamnesis, of the physical and laboratory tests, of the findings on laparotomy, and of the pathologist's reports upon tissues removed at biopsy. On account of certain difficulties in differential diagnosis with opportunity for a variety of opinions as to the precise nature of the patient's abnormalities, Prof. Kerr has asked me to devote the next hour wholly to a consideration of this rather unusual case.

CASE HISTORY (AS SUMMARIZED BY DR. R. HEINZ)

The patient, Sarah B., a white girl, age seventeen years, was admitted to the Medical Service of the hospital first on January 15, 1929.

Complaints.—Rupture; yellow skin from time to time; tenderness in and distention of the abdomen; occasional chills, fever, nausea, and pain in the upper right abdomen beneath the ribs.

Family History.—Negative, except that the women in her father's family all began to menstruate late. No history of jaundice or of diseases of the liver or spleen on either side.

Past History.—Tonsils removed at five; an attack of measles at six; otherwise healthy until the beginning of the present illness. Though she is seventeen years old, there has as yet been no sign of menstruation.

Present Illness.—For the past three years, it has been noticed that the patient's skin and eyeballs showed, at times, a yellowish tinge.

Two years ago, a hernia appeared suddenly in the right inguinal region; though it has not enlarged since, it is associated with a local dragging sensation.

For two months before admission, she had noticed that her abdomen was distended in the afternoon and was tender; during this time, she had four or five attacks, in which she had a chill, fever, nausea, and, occasionally, sharp pain in the right upper quadrant of the abdomen.

Physical Examination.—The positive findings included: Slight jaundice; slight enlargement of cervical lymph glands; slight increase of blood pressure (systolic 150, diastolic 90); distention of the abdomen with evidence of the presence of free fluid in the peritoneal cavity; right inguinal hernia; splenomegaly, the lower pole of the spleen being palpable 3 cm. below the costal margin; liver not palpable; hypoplastic breasts and uterus of infantile type; tendency to girdle obesity; slight tachycardia.

[1] Clinic in Toland Hall, University of California Hospital, Monday, November 25, 1929.

Laboratory Reports.—*Blood.*—On admission, red blood cells, 3,600,000; hemoglobin, 80 per cent; white blood cells, 4350 with 61 per cent polymorphonuclear neutrophil leukocytes; reticulated red cells 1.5 per cent; fragility test, 0.44 to 0.34 (within normal limits); icteric index 15. On March 26, 1929, red blood cells, 3,600,000; hemoglobin, 75 per cent; white blood cells, 4350.

Urine.—Faint trace of albumin; bile and urobilin present; no sugar; sediment contained a few white and red corpuscles and a few hyaline casts; phthalein output 65 per cent in first hour, 75 per cent at end of two hours.

Stool.—Negative.

Basal Metabolic Rate.—15.2 per cent plus.

Tentative Diagnosis on First Admission.—Splenomegaly with jaundice, ascites, and anemia (possibly hemolytic icterus, congenital or acquired, possibly Banti's disease); early arterial hypertension with slight renal disease; infantilism with genital hypoplasia and delayed menstruation; accelerated basal metabolic rate.

Transfer to Surgical Service.—On March 26, 1929, operation for hernial repair performed.

On April 4, 1929, reexamination of the *blood:* red blood cells, 4,000,000; hemoglobin, 60 per cent; white blood cells, 3160.

Urine.—Trace of albumin; no sugar; many casts; a few leukocytes.

Stool.—Negative.

Stomach Contents.—Free HCl, 16 acidity per cent; total, 40 acidity per cent.

Liver Function Tests (April 12, 1929).—Rose bengal retention at end of 8 minutes 100 per cent; at end of 16 minutes 100 per cent. Modified glucose tolerance test showed fasting blood sugar 0.09; after thirty minutes 0.111; after one hour 0.114; after two hours 0.062; insulin was then given and the blood sugar two hours later was 0.052.

Gallbladder Visualization Test.—Inadequate filling, probably pathologic gallbladder.

After careful consideration of all the findings on the medical and surgical services, *exploratory laparotomy* was decided upon, in order to ascertain the condition of the gallbladder, the peritoneum, the spleen, and the liver. The normal fragility test and the absence of familial history of jaundice were against the diagnosis of hemolytic jaundice; the anemia and the splenomegaly in association with ascites occurring in a young woman were strongly suggestive of Banti's disease, and indicated the possible value of splenectomy as a therapeutical measure.

Laparotomy.—On April 14, 1929, a laparotomy was performed. The abdominal cavity contained 4 liters of free fluid (transudate). The spleen was much enlarged. There was no evidence of disease of the peritoneum. The liver was small, hard, and coarsely nodular; two of the nodules had compressed the cystic duct with resultant hydrops of the gallbladder. The spleen was removed, as well as the nodules of liver tissue that had obstructed the cystic duct, the fluid in the abdominal cavity was removed, and the wound closed. The patient made an uneventful postoperative recovery.

Pathologist's Report on Tissue Removed at Biopsy (Dr. Charles L. Connor).—The spleen was very much enlarged; its appearance on section is shown in Fig. 9. On histologic examination of microscopical sections, the picture of the spleen was that of stasis due to portal obstruction.

Histologic study of sections of the liver nodules removed showed much regenerative activity, in association with the fibrosis of a coarsely nodular cirrhosis, suggestive of "toxic cirrhosis." After the operation, the urine contained no urobilin and another fragility test gave results within normal limits (0.40 to 0.30). *Conclusion:* Cirrhosis of the liver, probably of toxic origin; splenomegaly secondary to cirrhosis hepatis.

In the **postoperative period,** the wound healed satisfactorily, but ascitic fluid reaccumulated and the patient had to be tapped twice while still on the surgical service, 3400 cc. being removed on April 27th and 5100 cc. on May 3d.

Retransfer to Medical Service.—In early May, as the wound had healed, the patient was transferred again to the Medical Service for further observation. Examination of the *blood* now showed: Red blood cells, 3,370,000; hemoglobin, 70 per cent; white blood cells, 10,300; polymorphonuclear neutrophil leukocytes, 60 per cent; platelets markedly increased, many clumps seen.

Urine.—Trace of albumin; numerous hyaline and granular casts; recurring transient glycosuria.

Stool.—Negative, except for occasional occult blood.

The patient was placed upon a diet rich in carbohydrates and relatively poor in proteins, and 10 units of insulin were administered thrice daily.

The ascites continue to be troublesome, requiring paracentesis about once in ten days. Salyrgen (2 cc.) was given intravenously twice, but without any marked

Fig. 9.—S. P., 29, 1014. Case S. B. Splenomegaly secondary to toxic cirrhosis of liver.

effect upon the ascitic accumulation. Novasurol (1 cc.) was also given intravenously without apparent benefit.

The patient remained afebrile. The pulse rate continued to be accelerated, with rather marked fluctuations.

On discharge, the patient was to continue: (1) the diet rich in carbohydrates with limited protein intake and (2) the insulin injections. She was instructed to report regularly to Dr. Edgar J. Munter at the Out-patient Department for supervision and for occasional temporary admission for paracentesis.

Readmission to Stationary Clinic (November 11, 1929).—Throughout the summer and early autumn, the patient has had few complaints except the discomforts incident to the recurring ascites. Dr. Munter had found it necessary to tap the abdomen every two or three weeks. On admission she was tapped again and 10 liters of fluid

were removed. The urine has remained free from sugar, and on recent examination contained neither albumin nor casts.

DISCUSSION OF THE CASE

I can well understand the desire of the staff to arrive at a precise diagnosis in this case, since, particularly prior to the operation, the therapy to be adopted depended much upon one's conception of the relation, primary or secondary, of the disease of the spleen to the disease of the liver. If hemolytic icterus or Banti's disease were the cause of the splenomegaly, removal of the spleen might be advantageous for the liver; if the splenomegaly were due to stasis (portal obstruction), the removal of the organ could scarcely be expected to be of service, though it need not be harmful.

Nature of the Splenomegaly and of the Cirrhosis of the Liver.—We who study the patient today are fortunate enough to have before us the reports of the observations made at the laparotomy and the bioptic reports of the pathologist, so that our diagnostic problem is relatively simple compared with that by which the staff was confronted before the operation. Let us try for a few minutes to forget the findings at and after operation and to place ourselves in the position of the members of the staff during the preoperative period, considering only the data that were then available to them.

They knew that the spleen was enlarged and firm for they could feel it below the margin of the ribs. They knew that there must be some portal obstruction for there was free fluid in the abdomen and it had the characters of a transudate rather than of an exudate; moreover, they must have suspected that this obstruction was due either to portal cirrhosis of the liver or to pylephlebitis. They suspected some pathologic condition of the gallbladder because of the results of the visualization test. They could feel very sure that they were not dealing with a biliary hypertrophic cirrhosis of the Hanot type (if such a disease, in reality, exists), for the liver was not enlarged, the jaundice was slight and Hanot's cirrhosis does not cause ascites. They could also feel sure that they were not dealing with the cirrhosis of hemochromatosis for with it, too, there is enlargement of the liver and the skin becomes bronzed, whereas there was no bronzing of the skin of this patient.

Splenomegaly in association with hemolytic jaundice naturally came into mind early as a possibility, but was quickly ruled out by the absence of any family history of jaundice and especially by the normal findings on application of the fragility tests.

Primary splenomegaly due to Gaucher's disease, in which the spleen becomes enlarged owing to the accumulation in it of large cells filled with a clear hyaline substance (kerasin or sphingogalactoside), was also thought of, but would scarcely be considered long because of its rarity, on the one hand, and, on the other, because it is also exquisitely heredo-

familial in incidence, and, moreover, is accompanied by definite changes in the bones, changes not present in roentgenograms of the skeleton of this patient. The splenomegaly of leukemia and that of Hodgkin's disease could be ruled out by the blood findings and by the absence of any lymphadenopathy apart from the spleen.

The idea of the syndrome known as Banti's disease as a tentative diagnosis seems to me to have been easily justifiable, since enlargement of the spleen with outspoken anemia in a young girl is characteristic of the syndrome to which that name has been assigned. The studies of Banti in Italy, of Osler in America, of Hutchison in England, and of Senator in Germany long ago opened our eyes to the prevalence of this state and taught us the importance of early recognition since removal of the spleen before cirrhosis of the liver develops has seemed often to prevent the development of the secondary cirrhosis. In so-called Banti's disease, the first stage is characterized by an anemia of secondary type, occurring in a young person, and accompanied by marked splenomegaly ("toxic fibro-adenosis of the spleen"), this "splenic anemia" often lasting three, five, or even ten years before symptoms pointing to involvement of the liver set in. During this first anemic stage, febrile attacks at intervals are common, and the patient before us had such febrile attacks accompanied sometimes by chills, nausea, and pains in the right upper quadrant. Against the conception of this disease as originally formulated by Banti was the fairly good condition of our patient, despite the appearance of ascites due to portal obstruction; in the cases first described by Banti, the transition to the stage in which the signs of cirrhosis of the liver became evident was marked by an outspoken cachexia. Banti, later, however, described cases in which the transition stage, as well as the terminal cirrhotic stage, were markedly prolonged.

I must confess that I am among those who are very doubtful of the existence of any unitary malady that is responsible for the whole group of cases described in the bibliography as "Banti's disease" (or "primary splenomegaly with secondary cirrhosis of the liver"). Both clinical and pathologic-anatomical experience make one very skeptical of the existence of such unitary malady. Many of the cases described as Banti's disease have turned out to be instances of chronic pylephlebitis with secondary sclerosis of the spleen; other cases have been proved to be due to congenital lues of the liver and spleen, atrophic cirrhosis of the liver with stasis of the spleen, or toxic cirrhosis of the liver (in the sense of Mallory) with secondary splenomegaly. The name, therefore, if retained at all, ought to be applied to a "syndrome," with recognition of the fact that this syndrome may represent any one of several underlying pathologic processes. Still, in view of all the circumstances, it seems to me that the exploratory laparotomy upon this patient was justifiable and it was rewarding since it has gone far toward bringing clarity into the consideration of the possibilities of diagnosis where obscurity existed

before. We know now that we have to deal with a coarsely nodular cirrhosis of the liver that led to portal obstruction, ascites, stasis in the spleen, and splenomegaly. The operation relieved the pressure on the cystic duct that was causing hydrops of the gallbladder; and the removal of the spleen has done the patient no harm.

What can have been the cause of this coarsely nodular cirrhosis of the liver that exists in this patient. The amount of liver substance that has been destroyed must have been large if we are to estimate it by the degree of retention of the rose bengal dye used for testing the "total function" of the liver. The cirrhosis appears to fall in the group of the "toxic cirrhoses" in the sense of Mallory. It would seem probable that the febrile attacks with chills, nausea, and right hypochondrial pain must have represented exacerbations of some toxic or toxi-infectious process that from time to time caused necrosis of liver cells, perhaps a recurrent subacute yellow atrophy of milder form. But as to what this toxic process can be, we have as yet no clue. You have had cases here in which thyreo-intoxication seemed to be responsible for toxic cirrhosis of the liver; on the table before you is the liver from one such case, and if you will examine it at the end of the hour you will see the remarkable areas of regeneration that developed in the liver. Our patient's thyroid is slightly suspect, because of the persistent tachycardia, the slight arterial hypertension, and the slightly accelerated basal metabolic rate (15.2 per cent plus); but there is no struma, there are no eye signs; therefore it seems to me very improbable that there has been enough thyreo-intoxication here to permit us to hold it responsible for the recurring toxic liver damage. A search has been made for focal infections; but thus far nothing significant has been detected. The paranasal sinuses are clear. Roentgenograms of the devitalized teeth have been made and will be reported on later. As a dancer, the patient used some unguent for the purpose of whitening the skin; but on inquiry we find that its principal constituent was zinc oxide and we have been assured that it contains no arsenic or other substance that could be absorbed from the skin and exert a toxic effect. As yet, therefore, we must admit that the toxic factor concerned is entirely unknown to us.

The Nature of the Patient's Endocrinopathic Disturbance.—That the endocrine apparatus of this patient is, in some respects, functionally and structurally abnormal would seem certain. The syndrome pointing to slight overactivity of the thyroid gland (*hyperthyroidism*), I have already mentioned. The delayed puberty and the faulty development of the secondary sex characters point to defective internal secretion of the ovaries (*hypogenitalism*). When there is hypoplasia of the genital apparatus (as in this patient) one always thinks of a possible defect in the secretion of the hypophysis cerebri (*hypopituitarism*), and the suspicion thus aroused is further fed by the tendency she has shown to girdle obesity. Because of these suspicions, stereoscopical roentgenograms

of the sella turcica were made this morning and they are before you. You will observe that there is no enlargement of the sella turcica; there is rather a tendency to "shut-in" sella through the marked development of the clinoid processes. The occasional glycosuria may be due to beginning involvement of the islands in the pancreas (hypo-insulism), though I think it more likely to be due to disturbance of the function of the liver that regulates the sugar content of the blood. Let us be careful not to overestimate the importance of these endocrine anomalies. We can say that a *mild multiglandular endocrinopathic syndrome* exists—if you like, you may call it a hyperthyreo-hypogenito-hypohypophyseo-hypo-insular syndrome—but to assume that this has had anything to do with the origin of the patient's hepato-intoxication would be going much farther than we would be warranted in going in the present state of endocrinological knowledge. We need, too, to be very cautious in the diagnosis of multiglandular syndromes; as Hans Lisser has pointed out in Biedl's *Festschrift*, usually one glandular disease is predominant in such cases.

COMMENTS UPON THE FURTHER TREATMENT OF THE PATIENT

In the further management of the case it will be desirable to protect the damaged organs (liver, pancreas, kidneys) from burdens they are unable to bear. The liver will bear a diet rich in carbohydrates better than a diet rich in proteins and the demands made by a high carbohydrate diet upon the insular apparatus of the pancreas can be mitigated by continuing the small doses of insulin that have for some time been administered.

The anemia may be combated by diet and by the administration of iron compounds rather than arsenicals, since the latter might injure the remaining liver parenchyma. A very good mixture has the following formula:

℞ Liquor. ferri acetatis ..... ♏xv
Liquor. ammon. acetatis ..... ʒj
Aq. camphorae ..... ad. ʒij
To be given thrice daily.

The recurring ascites is the cause at present of most of the patient's discomforts. Provided there be no further recurrence of toxic injury (of this we can by no means be sure), the collateral circulation that has begun to develop may, in time, become sufficient to compensate for the portal obstruction. I remember a patient in the Johns Hopkins Hospital who had to be tapped over fifty times for ascites due to portal cirrhosis, but, finally, the collateral circulation became sufficient and the ascites ceased to recur. One must hope, of course, to do something by diuretics to lessen the ascitic accumulation, but, unfortunately, experience in this

direction thus far has not been fruitful since neither salyrgen nor novasurol had any appreciable beneficial effect. In a recent report (April, 1929) made by Dr. Rowntree, of the Mayo Clinic, I find the statement that in 75 per cent of the patients suffering from portal cirrhosis the ascites will yield to merbaphen and ammonium salts without the need of paracentesis or surgical interference. If this can be corroborated, a tremendous step forward will have been made in the amelioration of the condition of cirrhotic patients with recurrent ascites. In the same report, a suggestion is made for the prevention of hemorrhages from esophageal varices (the cause of death in about half of the patients who die from cirrhosis). Since McIndoe, in 1927, showed by injections of the portal system in cadavers (whose death had been thus caused) with gelatin and India ink, that the esophageal varices occur at the site of anastomosis of the coronary vein of the stomach with the intercostal, azygos, and diaphragmatic veins of the caval circulation, it was decided to try to block this main collateral channel so as to preclude the possibility of the portal blood reaching the esophageal varices. In May, 1927, Walters and McIndoe, in a case selected by Rowntree, operated upon a patient, ligating and dividing the gastrohepatic omentum and thus interrupting the flow of blood from the portal circulation through the coronary vein to the varices; the cut ends of the gastrohepatic omentum were sutured to the parietal peritoneum in the region of the falciform ligament of the liver in the hope of favoring the development of a collateral circulation through the paraumbilical veins to the cava. The patient made a good recovery from the operation and the hemorrages that had been occurring for some weeks (with blood in the stools daily) ceased. Ody, in Paris (1928), seems to have applied this method in the treatment of one case. It is, of course, too soon to be sure that this operation will insure patients against fatal hemorrhage, but we must hope that this new suggestion from the Mayo Clinic may in time be proved to be of value in preventing or, at least, greatly postponing the commonest mode of exitus.

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A DISCUSSION OF FIVE PATIENTS EXHIBITING CERTAIN FORMS OF MUSCULAR WASTING (PROGRESSIVE CENTRAL MUSCULAR ATROPHY AND PROGRESSIVE MUSCULAR DYSTROPHY)[1]

WE are fortunate enough this morning to be able to present in the clinic no less than five patients suffering from one form or another of progressive muscular disease with wasting.

CLASSIFICATION OF THE MALADIES ACCOMPANIED BY PROGRESSIVE MUSCULAR WASTING

The classifications of the diseases, accompanied by muscular wasting, or muscular atrophy, are somewhat complex and I have found in teaching medical students that it is preferable that they should begin their studies of the subject by learning to understand certain principles upon which classification should be based; and next they should learn how to recognize and to differentiate from one another cases belonging to the two great groups of disorders accompanied by muscular wasting, before troubling themselves too much with regard to the further division of each main group into its several subgroups. I have noticed, too, that at medical societies, many physicians have never learned the fundamental principles of differentiation between the two great groups referred to; one could see, at once, their confusion with regard to the two groups because of their lack of knowledge of the differential criteria.

In addressing you who are medical students, today, I should like to emphasize these criteria that distinguish the so-called "primary wasting diseases" of the muscles themselves (primary myopathies, or muscular dystrophies) from muscular wastings that are secondary to diseases of the nervous system (the progressive central muscular atrophies that are accompanied by lesions of the lower motor neurones and sometimes of the upper motor neurones in addition). Any disease of a lower motor neurone, be it in the peripheral nerve (neuritis) or in the anterior horn cells (poliomyelitis; progressive central muscular atrophy; gliosis of anterior horns) will be accompanied by a degenerative atrophy of the muscles innervated by the lower motor neurones that are involved. But the particular form of lower motor neurone disease that I wish to contrast with the primary myopathies or dystrophies, is the so-called "progressive (central) muscular atrophy," in which there is always a slow degeneration of the anterior horn cells in the gray matter of the spinal cord and, sometimes, too, in the cells of the motor nuclei of origin of the cerebral nerves.

[1] Amphitheater Clinic, University of California Medical School, December 9, 1929.

CRITERIA FOR DISTINGUISHING PRIMARY MYOPATHIES (DYSTROPHIES) FROM PROGRESSIVE (CENTRAL) MUSCULAR ATROPHIES

Among the criteria that are very important for the differentiation of these two great groups of progressive muscular wasting, I would emphasize: (1) The age of onset; (2) the distribution of the muscles in which the wasting occurs; (3) the presence or absence of fibrillary twitching; (4) the matter of familial incidence, and (5) the association or non-association with spastic phenomena.

1. **The Age of Onset.**—In general, *the primary myopathies (dystrophies) begin in infancy, childhood, or early youth, whereas the progressive (central) muscular atrophies rarely set in before middle life or later;* in some of the latter, particularly those in which the muscles innervated by the medulla oblongata become atrophic, the onset is usually after the age of fifty.

If you can *definitely* ascertain the age of onset in a given case you will have a helpful clue for placing the case in the great group to which it belongs. But the onset of these diseases is often so insidious that it may be difficult to determine the precise time at which it occurred. When the patients are first brought to the physician the disease may have already lasted for several years without having attracted any or much attention. Thus, one may see a patient in middle life who has, in reality, long had a muscular wasting due to a primary myopathy that was not suspected to exist, though if the patient had been examined carefully by an expert neurologist many years earlier the incipient malady might have been detected in the patient's 'teens or even in his childhood. But, keeping this possibility of error in mind, the report of onset of bilateral muscular wasting (in the absence of a history of poliomyelitis or of polyneuritis) as late as thirty or forty, suggests progressive muscular atrophy of central origin, rather than primary myopathy (dystrophy).

2. **The Distribution of the Muscles Involved.**—Though there are marked differences in each of the two great groups of progressive muscular wasting as regards the bodily distribution of the muscles that undergo the wasting, there is one fundamental rule that is very helpful in differentiating between the two great groups, and it is this: *In the primary myopathies (dystrophies) it is, generally, the muscles of the trunk, of the proximal portions of the extremities, or of the face that become weak and undergo wasting first, whereas in the progressive central muscular atrophies it is the most distal muscles of the extremities that are first and predominantly involved.* Thus, if, in addition to the youth of the patient, the onset of the malady be characterized by a waddling gait (due to weakness of the gluteal muscles), or by marked lordosis (due to weakness of the back muscles), or by wasting of the deltoids, and the muscles of the upper back with winging of the scapulae, or by wasting of the muscles of the

face, one can be fairly sure that he is dealing with a primary myopathy rather than with a progressive (central) muscular atrophy. On the other hand, if, in addition to the adulthood of the patient, the progressive wasting should begin in the small muscles of both hands or both feet, one can be almost certain that he is dealing with a progressive (central) form of muscular atrophy. It is in the latter cases that one sees the marked flattening of the thenar and hypothenar eminences of the palm of the hand, which gives rise to the appearance known as the "apelike hand" or the "simian hand." In these cases, too, on looking at the dorsum of the hand, one sees deepening of the intermetacarpal grooves due to atrophy of the Mm. interossi and the Mm. lumbricales. These facts, then, of early and predominant involvement of the proximal muscles of the extremities in the dystrophies and of early and predominant involvement of the distal muscles of the extremities in the progressive muscular atrophies of central origin are most important as differential diagnostic marks.

3. **The Presence or Absence of Fibrillary Twitching.**—*Fibrillary twitching in muscles that are undergoing wasting is an almost pathognomonic sign of an irritative process involving the cell bodies of the lower motor neurones (anterior horn cells in the spinal cord that give off the axones of the spinal motor nerves; large multipolar cells in the motor nuclei of origin of the cerebral nerves).* Even in muscular atrophies due to involvement of the peripheral motor nerves there is, as a rule, no fibrillary twitching, so that this sign helps also to differentiate between a central and a peripheral origin for the muscular atrophies that are due to diseases of the lower motor neurones.

But just as important is the *absence of fibrillary twitching in the muscles in the wastings that we ascribe to the primary myopathies (dystrophies).* If, in a patient whom you have suspected to be the victim of a muscular dystrophy, you should find an outspoken fibrillary twitching, you should question your tentative diagnosis at once, for in the majority of cases you will find that you are dealing with a muscular atrophy that has had its origin in disease of the central nervous system rather than with a dystrophy. There are some exceptions to the rule, but they need not detain us here. What is important at the beginning of the study of these great groups is to become familiar with the findings that are most common, rather than to consider the exceptional cases.

4. **The Presence or Absence of Familial Incidence.**—As a general rule, *the dystrophies are familial diseases* and *the progressive (central) muscular are nonfamilial* in incidence. It is not at all uncommon to have several sibs (brothers and sisters) in one family affected by the dystrophic muscular disease and, on inquiry, you may find that cousins of the patients also suffer from the same malady. In other words, the progressive muscular dystrophies belong definitely to the heredofamilial disorders. In progressive (central) muscular atrophy, in which there is

involvement of the distal muscles of the extremities or of the muscles innervated by the motor nuclei of the medulla oblongata and pons, occurring in persons of middle life or later, accompanied by fibrillary twitching, it is a single member of the family that so sickens. Here, again, I am ignoring certain exceptions (peroneal atrophies of the Charcot-tooth type; Werdnig-Hoffmann type), which, though they do not belong to the primary myopathies, may be familial in incidence.

5. **The Occurrence or Nonoccurrence of Spastic Phenomena.**—If you should find in a patient with progressive muscular wasting any spastic phenomena, such as ankle clonus, patellar clonus, or a positive Babinski reaction on stimulation of the sole of the foot, you will know that you are dealing with one of the forms of progressive (central) muscular atrophy and not with a dystrophy, for these *spastic phenomena point immediately to changes within the central nervous system (pyramidal tracts)*. They could not occur as a part of a progressive wasting of muscles due to a primary myopathy (dystrophy). This is not to say that a patient with dystrophy (primary myopathy) will never exhibit spastic phenomena, for even such a dystrophic patient might have an associated disease that involved the pyramidal tracts, but this would be a merely accidental association and not a part of the primary myopathy. Here, again, it is the general rule that I wish you to grasp rather than the exceptions.

Summary of the Principal Differential Criteria.—Let me summarize: In the *dystrophies*, the age of onset is in very early life. The distribution of the muscles involved is proximal in the extremities rather than distal. There is no fibrillary twitching. The incidence is often familial, and no spastic phenomena are observed.

On the other hand, in the *progressive (central) muscular atrophies* the age of onset is in middle or later life. The muscles involved in the extremities are the distal rather than the proximal muscles. The wasting is accompanied by fibrillary twitching of the muscles involved. There is, as a rule, no familial incidence. Associated spastic phenomena may sometimes be observed.

I believe that, if you will keep these few points in mind, it will be easy for you to place the majority of cases seen quite properly in one of the two great groups to which it belongs within five minutes after you see the patient, for these differential criteria are usually quickly ascertainable.

DIVISION OF LARGE GROUP OF THE PRIMARY MYOPATHIES (DYSTROPHIES) INTO SUBGROUPS

After you have learned, by the simple methods to which I have just adverted, to distinguish the great group of dystrophies from the great group of progressive (central) muscular atrophies, you will want to go still further and subdivide each group into its constituent subgroups.

First, let us consider the subdivision of the primary myopathies (dystrophies) into their subordinate categories. Here, again, the beginner should not try at first to differentiate all the subgroups from one another, but should pay attention especially to two principal subgroups; later on he may learn how to distinguish certain other less common and perhaps less important groups.

The two main groups of dystrophies to which I refer are: (1) The pseudohypertrophic paralysis of Duchenne and (2) the facio-scapulohumeral type of the primary myopathy, often spoken of as the Landouzy-Déjerine type of primary myopathy.

The Pseudohypertrophic Paralysis of Duchenne.—In this subgroup of the dystrophies certain muscles are enlarged throughout their whole extent. Thus the calves, the hips, and the buttocks especially, look excessively large, though the muscles of the upper extremities and of the trunk may look to be of normal size. The enlarged muscles are firm to the touch and elastic, though they may become somewhat softer later on in the disease. Despite this enlargement of the muscles (due partly to fat), the muscles of the lower extremities, of the pelvic girdle, and of the lower back are weak; the child tires easily and often falls on attempting to walk. Such children, on attempting to rise from the recumbent position, exhibit a peculiar behavior; first they turn upon one side, then get upon their knees, support the trunk by means of the hands, and, finally, "climb up their legs" to the erect posture.

The muscles of the shoulder girdles become involved so that these children have "loose shoulders"; if you place their arms by their sides and try to lift them from the axilla, they fall through their shoulders.

The Facioscapulohumeral Type (Landouzy-Déjerine).—In this type the pseudohypertrophy of the muscles, characteristic of the preceding type, is not present. The wasting begins in the muscles of the face in infancy so that the so-called *myopathic face* appears, the child looking apathetic and indifferent, with no wrinkling of the forehead and with lessening of the nasolabial folds.

Sometimes the lips are large and the upper lip projects (*tapir lip*). When the child smiles or laughs it is unable to elevate the angles of the mouth (*transverse smile*). Whistling and puckering of the mouth are impossible. Difficulty is experienced in pronouncing the labial letters. The eyes cannot be completely closed even in sleep (*lagophthalmus*), owing to weakness of the Mm. orbiculares palpebrarum.

The musculature wasting in the Landouzy-Déjerine type often extends to the muscles about the shoulder with wasting of the deltoids, the pectorales, and the muscles of the upper arm. Often, too, the muscles of the upper back become involved; owing especially to the atrophy of the rhomboid muscles, the scapulae cannot be held in close to the thorax, so that, if you ask the patient to stretch out his arms in front of him, the

scapulae will project behind like wings (*scapulae alatae*). Any wasting of muscles met with in the lower extremities will occur first in the region of the pelvic girdle. Often the muscles of the lower back are involved so that *lordosis* may be a prominent sign. In some patients of this type the so-called "wasp waist of Pierre Marie" may be met with (lower ribs vertical, waist contracted).

Less Common Forms of Dystrophy.—Those are the two main subdivisions of the primary myopathic group. If you wish to go still further, you may distinguish the *juvenile form of Erb*, which is like the Landouzy-Déjerine type, except that the face remains intact despite the scapulohumeral atrophy. You may also distinguish the *Leyden-Moebius type* (or the *Zimmerlin type*), which resembles the pseudohypertrophic paralysis of Duchenne in the distribution of the muscles involved, but does not show the same enlargement of the muscles. The juvenile form of Erb seems to stand very close to the Landouzy-Déjerine type, whereas the Leyden-Moebius type, and the Zimmerlin type would appear to be very closely allied to the pseudohypertrophic paralysis of Duchenne.

SUBDIVISION OF THE LARGE GROUP OF PROGRESSIVE (CENTRAL) MUSCULAR ATROPHIES INTO SUBGROUPS

Here four main subforms are to be distinguished, namely, (*a*) The spinal form of progressive (central) muscular atrophy; (*b*) the bulbar form of progressive (central) muscular atrophy; (*c*) the spastic form of progressive (central) muscular atrophy, usually called amyotrophic lateral sclerosis, and (*d*) the progressive neural form of muscular atrophy, sometimes known as "peroneal atrophy."

The Spinal Form.—In this form the anterior horn cells of the cervical enlargement of the spinal cord are first involved, leading to bilateral atrophy and fibrillary twitching of the small muscles of the hands (*Aran-Duchenne type*). The flattening of the thenar and hypothenar eminences with production of an apelike appearance to the hands is characteristic of this group.

The Bulbar Form.—Here the degeneration begins in the cells of the motor nuclei of the cerebral nerves and a slowly developing, but progressive bulbar paralysis appears. There is difficulty in speaking (*dysarthria*), difficulty in swallowing (*dysphagia*), and difficulty in chewing (*dysmasesia*). The lips become thin and the tongue looks spongy. In later stages the mouth may fall open, the lower lip hang, and the patient may drool.

The Spastic Form.—In this form there is degeneration both of the anterior horn cells of the lower motor neurones of the cervical enlargement, and of the pyramidal tracts in the lateral funiculi of the spinal cord. You have the clinical picture of an Aran-Duchenne atrophy combined with the spastic symptoms of lateral sclerosis. This condition is usually designated *amyotrophic lateral sclerosis*. It is probable that some of the

cases described in the literature as "primary lateral sclerosis" belong to the same malady, partially developed.

The Neural Form of Progressive Muscular Atrophy (or Peroneal Atrophy).—In this form it is the peroneal muscles especially that are involved, along with extensors of the toes and the small muscles of the foot with the development of *pes equinus* (or *pes equinovarus*). Later, the distal muscles of the upper extremities undergo atrophy and the so-called *clawhand* develops. The wasting of the muscles below the knee is often very striking (*bird leg*), whereas the proximal muscles of the extremities and the muscles of the trunk remain relatively unaffected. The peripheral nerves become thickened, hence the term "neural form." In this form there are also pains and other sensory disturbances in the lower extremities. Contrary to the general rule for progressive (central) muscular atrophies, familial incidence occurs. The exact nosological position of this type has been disputed; there are evidently lesions in the peripheral nerves, rather than primary lesions in the spinal cord.

PRESENTATION OF CASES

After this rather long introduction in which I have dealt with the general criteria for the classification of these wasting diseases of the muscles, I should like to present to you several illustrative cases.

ILLUSTRATIVE CASE I

Joseph I., a white Esthonian tailor, age fifty-five years, is a patient in the Laguna Honda Home. The history has been kindly furnished to me by Dr. S. B. Paul.

He entered the Relief Home some twelve years ago, and, at that time, it was stated that for over fifteen years he had been weak in the extremities and that this weakness had grown progressively worse. He had repeatedly fallen because of this weakness though he had never suffered any serious injury from his falls. He continued to work at his trade as a tailor up to the time of his entry into the home, but shortly preceding his entry he had grown much weaker and had tired very easily.

At the time of his admission (twelve years ago) it was observed that the muscles of all four extremities were weak, that the calf muscles were much enlarged, and that the scapulae were winged.

On physical examination, recently, the findings in the heart, lungs, and abdomen were negative, except for the fact that the diaphragm is paralyzed.

There is generalized weakness and atrophy of all the muscles of the extremities and of the trunk, but the muscles of the face have apparently not been involved. In the upper extremities, the muscles of the shoulders and upper arms are greatly wasted on both sides, but the musculature of the forearms and hands is well preserved.

The muscles of the lower back and of the pelvic girdle are weak and atrophic as are the muscles of the thighs.

There are no disturbances of sensibility, nor of the reflexes, except that the abdominals have not been easily elicitable and, on one occasion, one observer thought that the Babinski reaction was positive on the right.

There is no marked arteriosclerosis and the electrocardiogram shows only insignificant changes. *x*-Ray examinations of the skull and of the chest have been negative except that the diaphragm does not contract.

The patient is deaf in the left ear and is developing cataracts in both eyes.

In endocrine domains, he has a high-pitched voice, female type of distribution of body hair, and the testicles are undescended though they move freely in the canals. The basal metabolic rate is minus 16 per cent, the blood sugar content is 122 mg. per 100 cc. of blood.

You will note that the patient stands, supported by two canes, and, though he sits down from time to time, he spends a good part of each day standing in this manner. He can with great difficulty walk a little with the aid of his canes; but he makes progress with very short steps, very much like the gait of a patient with pseudobulbar paralysis (*marche à petit pas*). He often rests himself by leaning over the back of a chair for support, and, as you see, there is a broad callus across the upper abdomen, which has resulted from the oft-repeated pressure of the chair back.

You can see even from the back rows of the amphitheater that his face presents nothing very abnormal. The wasting about the shoulders and the upper arms is, however, pronounced, as is the wasting about the hips and thighs.

There is no fibrillary twitching in the muscles involved. On looking at his hands you see that the thenar and hypothenar eminences look normal; there is no Aran-Duchenne syndrome here.

Psychologically the patient is alert and intelligent. He is somewhat meticulous, and as you have noticed during the examination he is very particular as to just how he shall perform every movement that he makes. It is interesting to see how he reaches a percussion hammer across the table from him. You observe that he is unable to extend his arms in order to reach the hammer, but by resting his forearms on the table and putting the tips of his fingers upon the table in front of him, he can, with the fingers, pull by little jerks his arm toward the hammer, which he finally reaches.

You will, I am sure, have already placed the kind of muscular wasting presented by this man in the great primary group to which it belongs. The age of onset appears, it is true, to have been rather late, but the involvement of the proximal muscles of the extremities with preservation of the distal muscles, and the absence of fibrillary twitchings are criteria that are characteristic of progressive muscular dystrophy (primary myopathy). We have been unable, however, to secure any history of familial incidence. He has five brothers and three sisters who are said to be living and well. Only one brother is dead, and he died at birth.

I was interested in the history of a suggestive Babinski on the right side; but, as you see, when I stroke the plantar surface of the foot today there is no dorsal flexion of the great toe, so I think we can feel sure that there are no spastic phenomena present. The deep reflexes are indeed markedly diminished.

A very interesting feature of this case is the total paralysis of the diaphragm.

You will recall that when he entered the Relief Home, the muscles of the calves were noticeably enlarged, so we are probably right in placing this patient's malady in the subgroup of the dystrophies known as the pseudohypertrophic paralysis of Duchenne. It is a surprising thing that the patient has lived thus long.

Summing up the diagnosis in his case, the main features would seem to be the following:

1. Progressive muscular dystrophy (pseudohypertrophic paralysis of Duchenne).
2. Endocrinopathy with eunochidism, with retardation of the basal metabolic rate, and with hyperglycemia (hypothyreo-hypogenito hypoinsular syndrome).
3. Bilateral cataracts (perhaps to be associated with a chronic hyperglycemia).
4. Chronic otitis media (left), with unilateral deafness.
5. Psychasthenic trend, with tendency to overparticularity.

ILLUSTRATIVE CASES II AND III

The next two patients are sisters, M. S. and E. S., aged seven and two and a half, respectively, whom Dr. M. H. Hirschfeld has kindly brought to the clinic today. They illustrate exceedingly well the manifestations of one form of progressive muscular dys-

trophy that occurs in early childhood. The older girl is now greatly incapacitated; she is not able either to stand or to walk (Fig. 10). The musculature of the younger one is badly enough involved, but she still possesses more power in her muscles than does her sister. In these two girls it is the weakness of the muscles of the pelvic girdle, of the trunk and of the proximal portions of the lower extremities that is most pronounced, though the proximal muscles of the upper extremities are also already somewhat involved. The children at the onset fell often, owing to the weakness of the muscles about the buttocks and the hips. There is no fibrillary twitching and, strange to say, no evidence of hypertrophy or of pseudohypertrophy. The occurrence in two sisters is striking evidence of familial incidence, and I am told that one cousin also suffers from the same malady. The muscles of the face have not become involved in either child.

Fig. 10.—M. S., aged seven years, with advanced progressive muscular dystrophy Sister of patient in Fig. 11.

I hope that it will be possible to illustrate the peculiar method adopted by such a child as the younger one here on attempting to rise from the recumbent position. (To the child:) "Now you are lying on your back. I wish you would show us how you sit up and how you stand up." The child is a little negatively inclined and does not respond to my request. I will illustrate to you myself what would happen if the child would make the effort. The older child would willingly try to do so, but she is already too much incapacitated.

As I lie upon my back upon the floor, I turn first to my right side; then I get up on my knees and elbows, then rest my weight upon my hands and, gradually, by placing my hands upon my ankles, I grasp portion after portion of my lower extremities, ever a little higher, and thus I climb up my legs and thighs to the erect posture

(Laughter from the audience owing to the fact that the child, negative to request, had been positive to suggestion and had made almost exactly the same movements as the lecturer at almost precisely the same time.)

From what I am told, this child almost duplicated the illustrative movements that I, myself, made; but though the child imitated me, it was the desire to rise that actuated her; she is incapable of getting up from the recumbent position in any other way. Indeed, this mode of climbing up the legs is very characteristic of the muscular dystrophies (Fig. 11).

Now let us try the strength of the muscles about the shoulders. I shall attempt to lift each of these children by placing my hands in the armpits. You notice how each child "falls through her shoulders," owing to the great weakness of the muscles of the shoulder girdle. Neither is able to hold the shoulders down or close to the trunk.

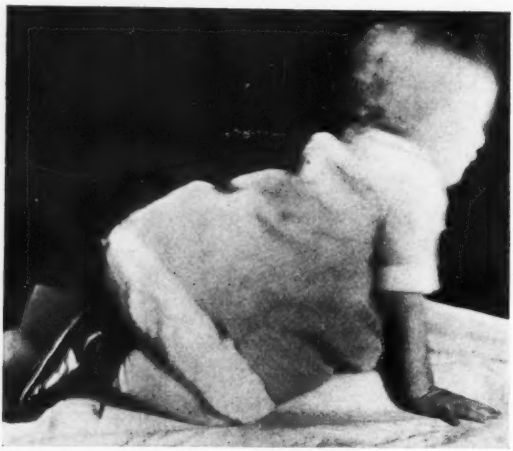

Fig. 11.—E. S., aged two and a half years, sister of patient in Fig. 10. Early stage of progressive muscular dystrophy. (Not entirely successful in getting patient to climb up her legs at the time the photograph was taken.)

Here, again, we are obviously dealing with progressive muscular dystrophy because of (1) the age of onset, (2) the distribution of the muscles involved, (3) the absence of fibrillary twitching, and (4) the familial incidence.

As to the particular subgroup to which these children belong, there might be some difference of opinion; but we shall have to place them, I think, in the category of Leyden-Moebius type, owing to the absence of any hypertrophy or pseudohypertrophy. It has always seemed to me, however, rather gratuitous to set up a definite subtype upon this basis alone and I feel sure that these children cannot be far removed from the pseudohypertrophic paralysis of Duchenne, even though the pseudohypertrophy of the musculature is lacking. Still, Nature does not lie; there must be some special reason why pseudohypertrophy occurs in some dystrophies and not in others! Perhaps, in the future, we may discover the reason.

ILLUSTRATIVE CASE IV

Peter S., age thirty years, a Porto Rican laborer, has been under treatment in this hospital at various times and for different reasons. In 1923 he was under treat-

ment for chancre, for pains in the groins, and for urethral discharge; at that time he was found, upon examination, to have both syphilis and gonorrhea. He was given thorough treatment for a time with arsphenamine and with local irrigations of the urethra. He made, apparently, a good recovery from the syphilis, for his Wassermann reaction has been known to be negative since 1926.

He has suffered from muscular weakness for at least eight years and I believe that had the development of the disease been suspected, a competent neurologist might have detected it many years before that. During the past two years he has had some infected warts about the perineum and rectum. He has been a vagrant who has sought relief at many different charitable agencies in the city. His brother states that he had a "funny walk" even in childhood and that he has always been a "queer egg" and unreliable.

He once fell 50 feet and had to be in the hospital for three months afterward. His tonsils were removed some six years ago.

On examination at the present entry he was found to be suffering from "vagabond's disease" (pediculosis corporis with many scratch marks) and the body in general was filthy. Heart and lungs were negative. Liver and spleen were not palpable. Five brownish warts (perianal) with generalized muscular weakness and wasting were the only physical anomalies observed.

Laboratory tests showed that there was no anemia and no urinary abnormality. The Wassermann reaction is still negative.

The patient has undergone a thorough cleansing process since he was admitted to the hospital and has had treatment with tincture of larkspur, vinegar, and shampooing. A mixture of alcohol, ether, and xylene were applied to the body after a cleansing bath and this was followed by still another tub. The sore areas were treated with liquid containing xylene and liquid petrolatum.

A psychiatric report has been made by Dr. V. H. Podstata, Professor of Psychiatry in the Medical School, who describes the patient's mental state as follows:

"As regards general capacity, the perception and associations of simpler type are reasonably effective. No sensory deceptions manifest. No serious memory defects, except those coincident with general inactivity of low grade (moron). No delusional trend noted.

"Emotional sphere presents nothing remarkable except that the patient seems to be rather indifferent. He is, however, aroused to anger when accused of stealing, and he cries when he dreams of his mother's death; but the prevailing mood is one of indifference. Volition is decidedly reduced, owing in part to actual motor impairment, in part to poor compensation and to general lack of initiative.

"From the standpoint of personality makeup, his physical constitution is asthenic. There is no personal advancement urge. He has no desire for marriage and, notwithstanding the history of venereal disease, no marked sex urge. Temperamentally, he presents nothing remarkable except a certain indifference to normal, everyday life influences.

"Intellectually he has not advanced beyond the immediate needs of life and is a moron.

"Character development has been very poor; he is lacking in inhibitions; he has no real ambitions nor any worthwhile aims in life."

You will have observed how helpful such a psychiatric report can be for the understanding of the mental deficiency and the characterological defects of the patient. The data mentioned will be useful in planning for the further care of this patient. It should be a rule that every patient who presents cognitive, affective or conative abnormalities should be carefully studied from the psychic as well as from the physical aspect, and this rule should be applied in private practice as well as in hospital wards.

Now, as we examine the musculature of this man, we notice that the muscles of his face are both wasted and weak. There is almost no wrinkling of the forehead and the nasolabial grooves, though still present, are not deep. When asked to show his

teeth, or to smile, he cannot retract the angles of the mouth and he exhibits the so-called "transverse smile." There is, however, no marked hypertrophy of the upper lip. There is extreme wasting of the muscles of the shoulders and upper arms, as well as of the muscles of the back. When I ask him to extend his upper extremities in front of him it is difficult for him to hold them even at a horizontal level and the scapulae cannot be held against the ribs but project backward (winged scapulae).

The proximal muscles of the lower extremities are also definitely involved. He waddles as he walks, owing to weakness of the Mm. gluteai medii, and he often falls.

Fig. 12.—P. S., a case of progressive muscular dystrophy of the facioscapulohumeral type.

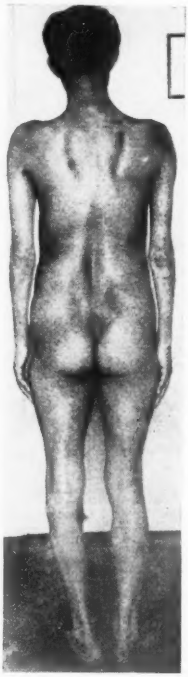

Fig. 13.—P. S., posterior view of patient in Fig. 12. Progressive muscular dystrophy of facioscapulohumeral type.

The deep reflexes cannot be elicited in either the lower or the upper extremities. No spastic phenomena are observable. No fibrillary twitching can be seen in the atrophied muscles. He holds his feet with the toes inverted, and, on walking, tends to rest his weight upon the lateral margins of the feet so that there is a definite tendency to pes equinovarus. The great toe is not, however, the toe of Friedrich's ataxia. The man is markedly undernourished (Figs. 12, 13).

Though we have no history of familial incidence, we are obviously dealing here with a progressive muscular dystrophy, that is to say, with a primary myopathy and I believe it to be of the Landouzy-Déjerine type, because of the early and marked

involvement of the muscles of the face, of the shoulders and of the upper arms. In addition, we are dealing with a patient who is a moron, whose poor cerebral development has been proved by his life of vagrancy, his lack of ambition, and his willingness to live in an indolent, filthy, and lousy state, seeking relief from the Salvation Army and other agencies, rather than attempting to make a living for himself. Medical men of Nietzschean trend might willingly see a patient of this sort develop a lethal streptococcal septicemia, or other malady that would lead to exitus, though medical men of Galilean trend would like the members of the Salvation Army to do what is possible to prolong and to ameliorate a pitiable existence.

ILLUSTRATIVE CASE V

Edward DeK., a white carpenter, age thirty-eight years, presents an entirely different history throughout childhood, adolescence and early adult life from any of the preceding four patients. He was very well except for childhood infections, for malaria at the age of seventeen and for influenza complicated by quinsy at the age of twenty-six. His tonsils were removed at the age of thirty-six. At this time he noticed that he was having difficulty with his right hand. He could not use it as well as formerly and he noticed that the muscles were wasting away. Some five months ago he observed that the power in his right leg was decreasing, and it soon began to drag.

Fig. 14.—Case of amyotrophic lateral sclerosis, patient E. DeK., showing the wasting of the small muscles of the hands.

A little later, the left leg became similarly affected. After that, the left arm became weak. He has had some cramplike pains in the extremities, but he has had no numbness, no tingling and no loss of sensation anywhere. He has become unable to walk because of muscular weakness in all four extremities and he has tired very easily on any exertion.

The general physical examination outside of the muscular and nervous systems was negative. The blood and urine were normal and the Wassermann test was negative.

On examination of this man's muscles you see a very beautiful example on each side of the "simian hand"; the thenar and hypothenar eminences are gone and the intermetacarpal spaces are greatly deepened (Fig. 14). He has almost no power of grip in either hand. There is a little tremor of the fingers and there is some atrophy of the muscles of the forearm with beginning atrophy of the muscles of the upper arm and about the shoulders. From time to time, one sees fibrillary twitchings in the biceps and the triceps muscles of the upper arms.

The atrophy and weakness in the lower extremities is less marked than in the upper, though the small muscles of the feet are somewhat atrophic and the muscles of the calves, as well as those on the fronts of the legs, are weaker and smaller in volume than normal. The right lower extremity is somewhat weaker than the left.

The deep reflexes in the lower extremities and in the upper extremities are exaggerated. As I stroke the sole of his foot you see, on each side, definite dorsal flexion of the great toe. There is, also, a well-marked bilateral ankle clonus, somewhat more pronounced on the left than on the right side. The pupils react to light and on accommodation. There is some deafness in the left ear, owing to a chronic catarrhal otitis media on that side. The cerebrospinal fluid has been examined and is said to be quite negative.

Here we have obviously to deal with a well-marked example of the other great group of cases in which muscular wasting occurs, namely, the group of the progressive (central) muscular atrophies. The late onset of the disease at the age of thirty-six, the bilateral involvement of the distal muscles of the hands with atrophy of the well-known Aran-Duchenne type, the fibrillary twitching in the muscles in the arms, all point to involvement of the lower motor neurones and particularly of the anterior horn cells in the gray matter of the spinal cord. But, in addition, the exaggerated deep reflexes with ankle clonus and the positive Babinski reactions prove that the pyramidal tracts have been bilaterally involved in the disease process. In other words, we have to deal with a typical example of the spastic form of progressive (central) muscular atrophy, often spoken of as "amyotrophic lateral sclerosis."

PATHOGENESIS OF THE PROGRESSIVE MUSCULAR WASTINGS

The etiologic factors in *progressive (central) muscular atrophy* are entirely unknown to us. The absence of familial incidence in these cases gives no clue to genotypic disposition, except in the peculiar Werdnig-Hoffmann group, to which I earlier referred. One cannot help, however, but suspect the existence of some congenital inferiority of the motor paths within the central nervous system, with resultant yielding in middle age to the ordinary wear and tear of life. The atrophy of the muscles in this group of cases is entirely secondary to the lower motor neurone degeneration; the muscle fibrils disappear, and electrical reaction of degeneration gradually develops as in all lower motor neurone lesions

As to the pathogenesis of the *muscular dystrophies* (primary myopathies) it now seems probable that we have in them to deal with a *defective genotypic pattern*, since a familial incidence is very common. Fortunately, we now have some good studies of family trees in this disease. Though there are several such studies available, the one that has impressed me most is that of Minkowski and Sidler (1928) who have studied the inhabitants of one of the secluded valleys in Switzerland where family records as far back as the 16th century are available. A careful analysis of these families has shown that for many generations no cases of muscular dystrophy occurred and then there was a *sudden explosive outbreak of muscular dystrophy* in the descendants of the family H and the family R, among whom there had been many intermarriages from the 16th century on. The eruption-like appearance of the disease among members of relatively numerous sibhoods after a period of multiple intermarriages, as well as the fact that the disease was not demonstrable among the direct ancestors of the patients, led Minkowski and Sidler to conclude that the dystrophy in these cases was *inherited according to the recessive mode in the mendelian sense.* Though the exact anal-

ysis of the inheritance process was exceedingly difficult because of the great number of intermarriages among relatives and because of the absence of cases in the direct ancestry, these authors have made certain deductions that seem to be valid. Since homogametes (that is, patients) in accordance with the recessive mode can only "Mendel out" on the basis of heterogamete marriages, they have felt justified in assuming that all the parents of the patients must have been provided heterogametically with the anlage (genotypic rudiment) of the disease. On analysis of the geneological trees, they found that all the parents of patients had been derived from the strains R and H and were blood relatives, and that the disease appeared only in children where each parent has been derived from both H and R strains. It was obvious then that in these cases of dystrophy there must have been a *double mendelian recessive process.* The trait could only become homogametic in the children mentioned (so that the disease could develop) if the parents who mated contained the two different pathologic genes heterogenetically in the same way. It would seem certain that in these cases the pathogenetic gene must have been present in these strains for at least three hundred years, so that the persons in whom the mutation started were living as far back as the middle of the 16th century. There was no evidence of sex-linked inheritance. The cases studied by Minkowski and Sidler appear to have belonged to the Erb-Duchenne type of dystrophy in which the muscular wasting began in the pelvic girdle.

Now, it is interesting that in certain geneological trees of families in which muscular dystrophies of the Landouzy-Déjerine type occur, the inheritance exhibited *mendelian dominance.* This appears to bring the proof that the Landouzy-Déjerine type of dystrophy is a totally different disease from the Erb-Duchenne type of dystrophy. Thus, studies of heredity have made it possible to arrive at a decision that helps in the nosological distinction of clinically similar diseases. Here again biology has come to the aid of clinicians in the making of clinical classifications. I pointed out to you the other day that in the differentiation of typhoid fever from paratyphoid infections, the clinical syndromes alone and the pathologic-anatomical findings alone had not sufficed for differentiation among the typhoidal group of diseases. It was only with the advent of bacteriological studies, that is to say, with the application of biological methods, that it became possible to prove that ordinary typhoid fever and paratyphoid fever were entirely different diseases. Once this so-called logical differentiation had been made by the biological method, clinicians were stimulated to investigate the clinical history of patients suffering from the typhoid and the paratyphoid diseases and became able to demonstrate certain differences in the clinical pictures. In the progressive wasting muscular diseases it is true that purely clinical studies had already shown the existence of different types of muscular dystrophies, but it remained for biological studies of heredity to prove that these

dystrophies were really entirely different from one another and followed a different mode of inheritance. These facts should be very encouraging to clinical investigators since they prove that slight differences in clinical pictures in diseases that, on the whole, are similar to one another are no accident; a diligent search for differences in causes and in pathogenesis should, therefore, be made in all instances where slight differences in the clinical pictures appear. I hinted at this in the discussion of the second and third cases when I said that nature did not lie. Our modern conception of patients as abnormal phenotypes, and our growing conviction that, in order to understand these abnormal phenotypes, we must study both the genotypic patterns and the environmental (paratypic) influences that have acted upon these patterns may here be emphasized.

The theory has been advanced that in the muscular dystrophies one link in the pathogenetic chain lies in a defect in innervation by the sympathetic nervous system. For some time we have known that the voluntary muscles of the body are doubly innervated; first, by the cerebrospinal nervous system (lower motor neurones) and, second, by fibers derived from the vegetative nervous system. The axones of the lower motor neurones from the cerebrospinal nervous system end in the well-known motor end-plates that lie upon the striated muscle fibers. The axones of the sympathetic nerve fibers, however, end in minute terminals in the sarcoplasm between the muscle fibrils. The theory has recently been advanced that, in the muscular dystrophies, owing to a defect of sympathetic innervation of the sarcoplasm of the muscle fibers, it disintegrates with resultant muscular atrophy. Though we must await further corroborative evidence of this view it seems to me highly suggestive. If this view should turn out to be valid, we could no longer look upon the dystrophies as primary myopathies, but would be compelled to regard them as of neural origin, though secondary to lesions of the vegetative nervous system, not of the cerebrospinal.

TREATMENT OF THE PROGRESSIVE (CENTRAL) MUSCULAR ATROPHIES AND OF THE MUSCULAR DYSTROPHIES

Heretofore, we have been greatly at a loss to do anything for either group of patients, except to protect the victims of these diseases from overexertion and to keep the general health at as high a level as possible. Recently, in the case of the dystrophies, it has been suggested that the atrophy of the sympathetic fibers might be due to insufficiency of the internal secretion of the suprarenal capsules, and that the regular administration of epinephrine might be helpful. This is now being tried systematically and in certain instances apparently with some benefit. It is also said that the administration of calcium is of some help in the slowing of the degenerative process. We must, however, have a much larger experience before we can be sure that these new methods of treatment are of any real value. For the present I am very skeptical.

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A CASE OF MYOTONIA CONGENITA (THOMSEN'S DISEASE)[1]

IN connection with the diseases of the muscular system that I have dealt with lately in one of this series of clinics, I wish to present to you this morning a patient who exhibits a very peculiar and a relatively rare form of myopathy.

CASE HISTORY

This patient, Emily G., was first seen in the Out-patient Department of this hospital on March 13, 1929. She is of Italian origin, forty-three years old, and a housewife.

Her main *complaint* is "inability to start muscular movements."

Family History.—Her father and mother are living and well at the ages of seventy-eight and sixty-eight, respectively. One of her sisters who died of heart trouble at forty-five had the same condition as the patient. Two of her brothers, age forty-five and thirty-two, are living and well. One cousin on her father's side suffers from the same condition as the patient. These 3 cases are all that have been discovered in the family history. It is stated that there has been intermarriage of relatives in this family. The patient herself has two children, a daughter of sixteen, and a son of six, both of whom are well and do not manifest any malady similar to that of the patient.

Past History.—Aside from some catarrh of the nose and throat and occasional gastro-intestinal upsets with constipation and gas, the patient has been very well except for her muscular symptoms and for late puberty and irregular menstruation. Menstruation began at seventeen and was very irregular. Her sisters gave a similar menstrual history.

Present Illness.—The patient states that her first memory of the muscular difficulty was when she was some ten or twelve years of age. One day her brother pushed her from behind and she was surprised to find that she could not move forward to right herself and she fell down. After this, she noted that she always had difficulty in starting to do anything, though, after a movement has once been begun, she thinks she can move as well as anyone. She says that on beginning the movement her muscles feel stiff and that, afterward, they seem to limber up. She has always been strong, and she has had no pain at any time.

Physical Examination.—It was found in the Out-patient Department that the patient had difficulty in rising from a chair and in taking off her coat, but she could remove her hat and her dress without apparent difficulty.

When asked to turn around suddenly, she found it difficult to do so. Examination of the chest and abdomen was negative. The pulse rate and blood pressure were normal, the deep reflexes were active except in the lower extremities where the knee jerks and ankle jerks could not be elicited, possibly owing to muscular tension. No abnormal reflexes could be elicited except for a doubtful Babinski on the left. Plantar stimulation on the right yielded plantar flexion, though on the left there appeared at times to be dorsal flexion of the great toe. On electrical test, the muscles responded promptly by contraction, but the contraction was maintained abnormally long and there was very slow subsidence of the muscle mass after rather rapid welling up (Dr. Lennon).

On **laboratory examination** there were no findings of importance. The Wassermann reaction was negative.

[1] Clinic in the Amphitheater of the University of California Medical School, December 9, 1929.

Present Condition.—I can demonstrate the main features of the patient's malady very quickly. On asking her to rise from the chair you notice the hesitation that precedes the movement. On asking her to walk across the floor and to turn abruptly she says she cannot make the turn quickly; there is always some delay. When I ask her to make a fist and then to straighten the hand out and to repeat these movements rapidly, she is utterly unable to perform the movements quickly. When I ask her why she does not do so more quickly she says that "the muscles hold fast" and will not allow her to make the movement. *This inter-*

Fig. 15.—Case of myotonia congenita.

ference with voluntary movements, due to rigidity that sets in upon attempting to make these movements, is very characteristic of this disease (Fig. 15).

In the second place I should like to call your attention to the size of her muscles. Though she is a woman, you will note that the thenar and hypothenar eminences are much larger than mine and when you look at the muscles of her forearms and of her upper arms you will see that they are larger than one would expect in a trained male athlete. This is true of the whole musculature of the body. *This hypervoluminousness of the muscles is just as characteristic, perhaps, of the disease as is the interference with voluntary movement from sudden rigidity.*

A third characteristic feature of the disease is the behavior of the muscle masses on electrical stimulation. *The tonic contraction that results from stimulation of the nerves supplying her muscles shows a peculiarly long persistence (myotonic reaction of Erb).*

In the fourth place, it is extraordinary that, despite this hypertonus of the muscles that sets in on innervation, there is in this patient loss of knee jerks and of the ankle jerks. This occurrence of *areflexia* in this disease has been noticed in other patients.

Some patients with myotonia congenita, or Thomsen's disease, for that is the name of the malady we are observing, suffer from epilepsy, migraine, or progressive muscular dystrophy. In this patient there has been no sign of any of these maladies. The only abnormal sign is a suggestive Babinski on the left, a point that is to be investigated further.

It is impossible for these patients to inhibit the kind of hypertonus that occurs by the exertion of will power. A practitioner unacquainted with the disease might make the error of thinking he had to deal with an hysterical phenomenon, but anyone familiar with the malady would recognize it immediately upon the making of a few simple tests. The fact that the same persistence of the tonic muscular contraction occurs on electrical stimulation as on voluntary contraction rules out a psychic origin; the phenomena are quite outside of the will power and the morality of the patient.

Usually the whole musculature of the body is enlarged and contractions of all the muscles are associated with the abrupt hypertonus mentioned. In some cases even the eye muscles have been involved. The motor disturbance is accentuated by excitement or by exposure to cold.

The disease does not shorten life, but, unfortunately, it has not been found amenable to any form of treatment thus far tried.

If a piece of muscle be excised you will find, upon examining it, that there is hypertrophy of the primitive fibrils and an increase of the sarcolemma nuclei.

The disease is one of the heredofamilial maladies; this patient was born with an abnormal genotypic pattern. A careful analysis of family trees should be undertaken with the object of determining the mode of inheritance in the mendelian sense.

One ought to be on the lookout in patients of this sort for the special form of myopathic dystrophy that sometimes accompanies Thomsen's disease. It has been designated atrophic myotonia and has been met with most often in patients between the ages of twenty and thirty. In some cases the atrophy is limited to the muscles of the hands, forearms, shoulders, and face. It is associated, as a rule, with general emaciation, with loss of knee jerks, with some disturbance of speech, with the occurrence of cataracts, and, in males, with atrophy of the testes. Though this patient has shown no signs of muscular atrophy it is interesting that

she menstruated very late, a symptom that is suggestive of ovarian hypoplasia.

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DIAGNOSIS AND TREATMENT OF THE PARKINSON-LIKE SYNDROMES OF CHRONIC EPIDEMIC ENCEPHALITIS[1]

DURING the past ten years medical practitioners have been forced to become familiar with a disease that was formerly entirely unknown to them, but which, during the period mentioned, has become a very common malady, occurring not only in great epidemics but also sporadically. I refer to epidemic encephalitis. By chance, the opportunity came to me to be among the first to observe cases of this disease in America, soon after the epoch-making publication of von Economo in Vienna. The disease spread rapidly, as you know, and its occurrence in epidemic form soon made most practitioners familiar with the acute types of the disease. Strange to say, however, the malady assumed a somewhat different type in different epidemics. Thus, in the first outbreak, we saw, most often, the *somnolent-ophthalmoplegic form*, described by von Economo as "lethargic encephalitis," characterized by pathologic drowsiness, eye-muscle paralyses, and fever. In later epidemics, we became familiar with *hyperkinetic forms* of the acute disease, particularly the *myoclonic form* and the *choreatic form*, in which there were muscular twitchings or choreiform movements, respectively. Very often, in these, twitchings of the abdominal muscles were met with as an initial symptom and, sometimes, a twitch of the diaphragm, causing hiccup, gave a clue to the presence of the malady. In still other epidemics, acute stages of still other sorts were met with (ataxic cerebellar form; meningeal form; radiculitic form; polyneuritic form).

For the extension of our knowledge of this remarkable disease, it was fortunate that these different types of the acute stage of the malady were met with in epidemics, for had they been encountered only in sporadic cases, it would have been scarcely possible to have been sure (without postmortem examination at any rate) that we were dealing with different types of one and the same disease.

As time passed, we became acquainted gradually with still other clinical pictures of epidemic encephalitis that deviated from the main clinical types and we were forced to recognize that epidemic encephalitis could, in its manifestations, simulate almost any malady of the central or peripheral nervous system, according to the particular part of the nervous system in which the virus or toxin that causes the disease becomes localized. Moreover, as still further time elapsed, internists and neurologists were greatly surprised at the extraordinary frequency of what were called "sequels" of the disease (after the acute stage had passed and some weeks or months of relative quiet had intervened).

[1] Amphitheater Clinic at the University of California Medical School, December 16, 1929.

We began to meet with the peculiar Parkinson-like syndromes that are now so well known. The faces of the patients assumed a masklike expression, general rigidity of the musculature developed, and there was loss of the well-known associated movements, like the swing of the arm on walking, and the dorsal flexion of the wrist on making a fist. In other words, we found in these cases marked evidences of involvement of the extrapyramidal motor system. In another group of late cases we met with syndromes that closely resembled some of the well-known classical endocrinopathies, for example, dystrophia adiposogenitalis, diabetes insipidus, and Basedow-like pictures. Some of these latter cases came to autopsy and where found to be due not to endocrine disease but to involvement of the vegetative nerve centers at the base of the brain, especially of the hypothalamus.

Closer attention then came to be paid to the period that intervened between the acute stage of the malady and these later syndromes to which I have referred and it was found that, though the patients had passed through a relatively quiescent stage, most of them had not been well. They had exhibited disturbances of sleep, peculiar forms of nervousness, fatigability and emotional symptoms that would ordinarily be, classed as "neurasthenic" phenomena.

Gradually, the pathologic anatomists had opportunities to examine the nervous systems of patients who had died in one or another of these several stages, and it soon became clear to them that epidemic encephalitis ought not to be regarded as an acute disease with sequels, but rather as an exquisitely chronic malady that may last not only for months, but for years. Most of the cases showed an acute onset in the form of an infectious febrile disease (sometimes influenza-like), but, in many patients, the acute manifestations were so slight as to go almost unnoticed, whereas, later on, the typical manifestations of one or another of the later stages became easily recognizable. In some cases, fortunately, the disease is much milder and less chronic than in others; indeed, in many cases a complete cure seems to follow the acute stage without the development of the symptoms of the chronic stages. But initial mildness is no guarantee of subsequent indemnity from a severe chronic stage; I have seen many people virtually ruined by a chronic encephalitis that began with symptoms that were relatively trivial.

We do well, therefore, to think of epidemic encephalitis as consisting of three different stages: (1) The *acute stage* with fever, with leukocytosis as a rule, and with one or another of the syndromes common in this acute stage (somnolent-ophthalmoplegic; myoclonic; choreatic; ataxic; meningitic; radiculoneuritic; abortive, etc.); (2) the *relatively quiescent stage* or *pseudoneurastheniform stage* lasting for weeks, months or even years, and (3) the *late chronic stage*, with syndromes formerly regarded as sequels (Parkinson-like and other extrapyramidal motor syndromes; endocrinopathiform syndromes; vegetative neuroses).

This morning I am permitted to show you three patients (from Prof. Kerr's service in this hospital) that illustrate very well the parkinsonian features so often observable in the third (myastatic) stage of the disease. I shall ask Dr. Evelyn Anderson to summarize the clinical histories of these patients, after which I should like to comment upon the diagnosis and the differential diagnosis in such cases, as well as upon the therapeutical management.

CASE I

Margaret T., age twenty-five years, has been under observation in the Out-patient Department of this hospital since September, 1927, when she came with the *complaints* of "nervousness" and "tremor."

The **family history** is negative, except that the mother died at fifty of cancer.

Previous History.—The patient has always lived in California and was educated as far as the end of the first year of high school, since then she has kept house for her father. She had measles at five and an attack of influenza at fourteen (1918). At twenty-one her tonsils were removed and this operation was followed by considerable hemorrhage. She has had occasional headaches, some palpitation of the heart, some gaseous indigestion, and a rather scanty flow at the menstrual periods. She wears glasses for reading. Her appetite has been poor, and she is somewhat underweight.

Since her eleventh year, she has suffered from occasional fainting attacks in which she gives a scream, becomes unconscious and bites her tongue. Following upon the attack, she suffers from frontal headaches.

Present Illness.—In 1918 (eleven years ago), when the patient was fourteen years old, she had a mild attack of "influenza," being sick some three or four days; convalescence was reported as uneventful. However, some four years later it was noted that she was very weak and nervous and that her movements were becoming markedly slow. (It is probable that the neurologists could have observed symptoms earlier than this.) She, herself, noted that she muddled her words when speaking. Later, a tremor developed and it was especially noticeable in her hands when eating.

On **physical examination** in 1927, she was markedly undernourished, the face was rather immobile and her mental responses seemed slow. Her posture was reported as good, but there was slight propulsion of the gait. Her pupils reacted normally, the eye grounds were negative; there was no nystagmus. There was, however, coarse tremor of the tongue. Examinations of the pharynx and of the chest were quite negative. The pulse rate was 72, the blood pressure was 116 systolic, 82 diastolic. The abdominal muscles were rigid but the abdominal examination was otherwise negative.

In the extremities there was rigidity and weakness of the muscles of the right arm and tremor of the extended fingers on both sides. The deep reflexes were somewhat exaggerated, but they were equal on the two sides. The Babinski test was negative on both sides. Romberg negative.

In the Out-patient Department the diagnosis of parkinsonian syndrome following upon epidemic encephalitis was made by Dr. Lennon and the patient has been kept under observation since 1927, receiving courses of sodium cacodylate injections at intervals. The dispensary records do not report, however, any marked improvement in the condition of the patient.

Let us examine this patient now and see what symptoms and signs are demonstrable. At first glance you can scarcely fail to notice the apathetic, expressionless look of her face. She holds her head in a rather fixed position, inclined toward the left side. There is marked diminution

of all spontaneous movements, and when she makes movements they are slow (bradykinesis). When she walks her gait is "stiff" and you will observe that, though she swings her left arm on walking, the right upper extremity does not swing at all (loss of associated movement of the right arm on walking). She does bend the hands dorsalward on making a fist, so those associated movements are still preserved. As she talks, the words are articulated slowly and the speech is monotonous (without modulation). There is tremor of the fingers, but it is a far less coarse tremor than one usually sees in lesions of the extrapyramidal motor system. The face looks greasy and she sweats freely. The overactivity of the sebaceous glands and of the sweat glands is common in these cases. There is overproduction of saliva (sialorrhea), and sometimes she actually drools. I am very much interested in the unilateral predominance of the rigidity syndrome in this patient; the hypertonicity is much more marked on the right.

The criteria for the diagnosis of a parkinsonian syndrome in this case are manifest enough. The masklike face, the muscular rigidity without lesions of the pyramidal tract, the slowing up of the movements, the disappearance of the associated movement of the right arm on walking, which should normally be present, the tremor of the tongue and of the extended fingers are all characteristic of disturbances in the domain of the extrapyramidal motor system.

When you have such an extrapyramidal motor syndrome (with the Parkinson-like picture) appearing in a young person, its cause, in the vast majority of cases, is a preceding encephalitis. In this case, there is a history of influenza that developed some four years before the present symptoms were reported, though, as I have said, it is probable that an expert neurological examination might have revealed extrapyramidal motor symptoms earlier. As you know, the first stage of an encephalitis in mild cases may be represented only by a condition that is diagnosed as an "influenzal attack."

There is one point, however, in the history that should give us pause. I refer to the occurrence of epileptiform seizures in this patient since the age of eleven. Though her epilepsy is probably of the so-called "idiopathic" type, one must always keep in mind the possibility of a brain tumor. Moreover, a brain tumor occurring in the region of the basal ganglia could give rise to a Parkinson-like syndrome. This, however, is exceedingly rare. I think that we are justified, in this case, in assuming that a chronic myastatic encephalitic process has been superimposed upon the epilepsy of unknown cause. In other words, the association of epilepsy and encephalitis would seem to be accidental.

CASE II

The second patient, Julio M., has been under observation in the Out-patient Department since November 2, 1927. He is a Mexican cigar maker who has lived in this city since he was thirty-five years of age. He is now fifty-two years old.

When first seen two years ago, his *complaints* were of tremor of the right side and of the left hand, with moderate rigidity of his muscles.

His **family history** throws no light upon the case, though his father was alcoholic.

In his **past history,** he had smallpox at five and he also had measles in childhood. He had malaria at thirty-four. Venereal diseases were denied. He has never been operated upon, except for an abscess on the left side of the neck as a small child. His habits have been good as regards the use of alcohol, tobacco, and coffee. He formerly weighed 180 pounds but during the three years between 1924 and 1927, he lost over 50 pounds in weight.

Present Illness.—In 1921 the patient had an attack called "influenza," when he was very ill for eight days, had high fever and aching pains over the body, as well as diplopia. This was evidently the acute stage of an encephalitis. In the spring of 1925 (about four and a half years ago), the patient suffered from weakness in the arms and legs, and soon after this began to notice shaking of the arms and coarse tremor of the fingers.

One week before application to the Out-patient Department, in 1927, tremor of the right foot had begun, and he noticed that his foot kept up a tapping movement upon the floor when he was seated.

On **physical examination** in November, 1927, there was marked stiffness of the gait with a tendency to walk faster as he progressed and also to fall forward (festination and propulsion). His face was smooth and devoid of expression and there was slow tremor of the head. The skin was delicate and white and the mucous membranes were of good color. The pupils were equal, round, and regular. The extra-ocular movements were normal, but the pupillary reflexes (both for light and on accommodation) were sluggish. It was difficult to see the eyegrounds because of the coarse tremor of the head but no marked changes could be made out in the optic disks. In addition to the marked tremor of the head, there was some tremor of the tongue, a constant pill-rolling type of tremor of both hands, tremor of the arms, and tremor of the right leg and of the right foot. There appeared to be some wasting of the muscles of the arm. Dental hygiene was poor. The tonsils were small and infected. The thyroid was firm, but not enlarged. The chest was emphysematous and a few râles were audible at the bases (bronchitis). A systolic murmur was audible in the mitral area; the pulse rate was 90. The blood pressure was 144 systolic, 94 diastolic. There was generalized muscular rigidity and slowness of all voluntary movements. The deep reflexes were all active, those in the triceps and biceps being somewhat hyperactive. The diagnosis of a postencephalitic parkinsonian syndrome was made and the patient was followed in the Out-patient Department subsequently.

He received a subcutaneous injection of sodium cacodylate twice a week during several periods and was given advice about general hygiene.

On examination today, eight years after the onset of his acute encephalitis, the patient presents a *typical picture of the third stage of chronic epidemic encephalitis with Parkinson-like rigidity* (Fig. 16). There is marked, coarse tremor of both hands with characteristic pill-rolling movement. The latter is more common in "true" paralysis agitans than it is in the parkinsonism of chronic encephalitis. You notice that, as he sits there, his right foot keeps moving up and down; this is a coarse tremor of the lower extremity that parallels the coarse tremor of the hands. There is generalized rigidity of the musculature of this man; on making passive movements, I can elicit a typical "cogwheel phenomenon," as the resistance is overcome.

You have heard him just now replying to my questions and you must

have been struck not only by the lack of modulation of his voice, but also, and particularly, by the extreme bradylalia that he exhibits. He has lost the associated movement on making a fist with his right hand and also the right arm does not swing at all as he walks, the left but little. His face, too, has a greasy look and saliva sometimes flows from his mouth. Note his disinclination to perform even those acts of which he is capable.

Fig. 16.—J. M., parkinsonian syndrome, following epidemic encephalitis.

That this Parkinson-like syndrome is due to chronic myastatic encephalitis and not to other causes would seem very clear, for the history seems to be unequivocal. In the first place, he went through an acute stage with typical symptoms of the somnolent-ophthalmoplegic type of the disease. Then, he had a period when he was "perfectly well," according to reports. This corresponded to the second or relatively quiescent stage of the disease. Most patients during this second stage present neurastheniform symptoms. This patient speaks English very

poorly and he was not observed by any of the staff during the period when he was said to be perfectly well. It is quite possible that, if he had been examined during that period, certain stigmata of the pseudo-neurastheniform stage might have been discovered. After the quiescent stage, the typical symptoms of the third stage appeared (tremor; rigidity; hypokinesis; and bradykinesis).

CASE III

A third patient came in this morning unexpectedly. I shall deal with his case briefly. This young man is twenty-three years old. He first came to the Out-patient Department two years ago, complaining of weakness in his right arm and leg. He suffered an acute illness ten years ago (in January, 1920), which lasted for three months.

The *onset* of the illness was quite sudden. He had high fever and suffered excruciating pains in his arms, shoulders, and legs. He had an eruption on his left leg, which was diagnosed as "shingles." For the first three weeks of the acute illness he was unable to sleep at all. After that he slept in the daytime and was awake all the night (so-called "inversion of sleep"); during a part of the time he was delirious.

Following the "shingles" in his left leg, a dull ache continued in that leg, but there was a complete loss of pain sensation in his left foot. Sores developed on his toes very soon. There was some sloughing of the tissues and spicules of bone were extruded, which the patient was able to remove himself because of the absence of pain. These open lesions on his toes remained for some eight years until October, 1928, when the toes were amputated, with subsequent healing.

Eight months after the onset of this acute illness he noticed that his right leg dragged when he walked, and that he tended to hold his right arm rigidly flexed at the elbow. Since then a tremor has developed in this arm and leg. One year after the acute illness he noticed a change in his speech. There was a slurring of the words and a lack of modulation of the voice.

The significant findings upon **physical examination** are as follows: The patient is a tall, well-nourished young man of twenty-three. His face has the typical parkinsonian mask. He holds his head inclined to one side. He walks with his right leg held rigidly flexed at the knee, so that for practical purposes it is shorter than the left leg and causes him to limp. He holds his right arm with the elbow flexed (Fig. 17). When seated and at rest there is a slow rhythmical tremor of his right arm and leg. He speaks with a slow, halting, monotonous voice, which is consistent with his expressionless face.

His skin is of fine texture and somewhat oily (seborrhea). His left foot is damp with perspiration. There is a coarse tremor of his tongue. The heart and lungs are negative. The blood pressure is 126 systolic, 84 diastolic. The abdomen is negative.

On his left foot only the proximal phalanges of the toes remain. There is a clean amputation scar. The right arm is flexed at the elbow and the right hand droops. The right leg is flexed at the knee. There is considerable muscular rigidity on the right; the left arm and the left leg can be fairly well relaxed. The deep reflexes on the right are at first difficult to elicit, but when obtained they are very lively. Those on the left are lively and are easily obtained. Only the lower abdominal reflexes can be elicited. Babinski is negative on both sides. Romberg is negative. There is some adiadokocinesis. Touch sensation is normal over the entire body. Pain sensation is, however, decreased on the right side of the face, over the right hand and foot and over the lower third of the right leg; it is entirely absent over the lower third of the left leg and foot. The blood Wassermann is negative. The cerebrospinal fluid has not been examined.

For the past two years, the patient has been on 1/100 grain of hyoscine hydro-

bromide three times a day. He has been coming to the clinic twice a week for injections of sodium cacodylate. He is still able to carry on his work (selling newspapers).

In this patient we have to deal also with chronic (myastatic) encephalitis. The hypokinetic, hypertonic, bradykinetic syndrome is much more marked in the right

Fig. 17.—U. H., Parkinsonian syndrome in man twenty-three years old, following epidemic encephalitis ten years earlier. Right arm and leg rigid.

half of the body than in the left. He has marked analgesias and hypo-algesias on both sides of the body. His symptoms have been mitigated by the administration of hyoscine.

COMMENTS UPON THE DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF CHRONIC ENCEPHALITIS

The diagnosis of encephalitis in the *acute stage* is very easy, as a rule, during epidemics, but it may often be extremely difficult when the disease is not epidemic. The same is true of the second or *neurastheniform stage* of the disease. But, the *third stage* of the disease is usually far easier of diagnosis than either the acute preliminary stage or the second pseudo-

neurastheniform stage. Certain difficulties there are in some cases, but it is relatively rare to find the difficulties insuperable, provided a very careful history is taken and a thorough general physical examination made.

The diagnosis of the third stage is particularly easy in young persons; it may be somewhat difficult in persons who are older, for reasons that I shall give you in a moment. Anyone who is familiar with disorders of the extrapyramidal motor system, particularly with parkinsonian syndromes, will make the diagnosis almost at a glance in younger persons and the diagnosis will be fully corroborated if, on recording the anamnesis it be found that the patient has a few months, or even a few years, earlier suffered from some acute infectious disease with fever that was accompanied by one or another characteristic symptom of the acute stage (drowsiness, diplopia, eye-muscle paralysis, hyperkinetic phenomena).

It is true that before general practitioners became acquainted with the Parkinson-like pictures that follow upon epidemics of encephalitis, mistakes were sometimes made. I can remember cases that were brought to me by family physicians who supposed that their young patients must be hysterical or that they were in the early stages of a hebephrenic or catatonic dementia praecox. Thanks to the many clinics that have been held upon such patients and to the rich literature upon the subject, the general profession is now much better informed regarding these late stages of epidemic encephalitis. For a time, indeed, there was some danger of the diagnosis being made too often, since it had become "fashionable." As the possibility of this error was pointed out, many practitioners again became, at times, too doubtful about making the diagnosis of encephalitis when it should be definitely made and, at the present moment, there are many who are so fearful of confusing chronic encephalitis with some other condition that simulates it that they fail to make the diagnosis when it is fully justifiable. But if one will but keep in mind the importance of considering the history and the course of the disease (*i. e.*, the "longitudinal section"), as well as the "transverse section" of it met with at a given time, error of diagnosis can nearly always be avoided.

There are clinical pictures that resemble the third stage of epidemic encephalitis that can be definitely shown to be due to something other than the disease under consideration. In other instances, though the "transverse section" of the disease may make one strongly suspicious of encephalitis, the history may be so incomplete or so indefinite that one will do well to keep his mind open regarding the actual nature of the disease process until the patient has been longer observed. As I have said, epidemic encephalitis may give rise to symptoms that may imitate almost any one of the many organic diseases of the central and peripheral nervous systems; and if a general practitioner has had but little experi-

ence with the disease and, particularly, if he has not been well trained in clinical neurology, he should, when in doubt, seek the aid of a skilful neurological consultant. In the more obscure cases, even neurologists who have been thoroughly trained and who have had wide experience with chronic encephalitis may sometimes be compelled to admit of difficulty in arriving at definite diagnoses.

When confronted by clinical pictures that point to involvement of the extrapyramidal motor system, one should always keep in mind the possibility of a preceding encephalitis, but he should also not forget that such clinical pictures may, in some cases, have a nonencephalitic origin. This is particularly true of the bradykinetic-hypertonic syndrome, for the slow movement and the muscular rigidity without signs of involvement of the pyramidal tract may be due to chronic cerebral vascular disease, to cerebral neoplasm, or to still other maladies of the central nervous system. The coarse tremor and the pill-rolling movement of the thumb and index finger, though they point to diseases of the extrapyramidal movement system are not necessarily due to chronic encephalitis. In *true Parkinson's disease*, which appears in people of middle life or in older persons, this tremor may be present along with the parkinsonian mask, the slowing of movements, the general muscular rigidity, and the peculiar gait (with propulsion, retropulsion, or lateropulsion). The tremor in the encephalitic cases is, as a rule, somewhat different from that of true Parkinson's disease; and it is often associated with the "cogwheel phenomenon" on testing passive movements in the upper extremity. Nevertheless, I should not want to rely upon the character of the tremor alone as a differential diagnostic point. Certain disturbances of the vegetative nervous system, especially sweating, drooling because of sialorrhea, and a greasy condition of the skin, are more common in encephalitis than in true Parkinson's disease, but they may be met with in the latter. However, in most cases in which the skin is very greasy, the drooling is pronounced, and the secretion of the lacrimal glands is increased with epiphora, the diagnosis of chronic stage of epidemic encephalitis is the more probable. And if the Parkinson-like syndrome be accompanied by other symptoms referable to disease of the corpus striatum, particularly in the form of complex hyperkinetic phenomena, with repetition of movements that have an automatic character, the diagnosis of chronic epidemic encephalitis is strongly favored. Among the automatic movements that frequently recur in chronic encephalitic cases I may mention smacking of the lips, snout cramp, frequent compulsory swallowing movements, the production of peculiar snorting sounds, and certain peculiar uncomfortable attitudes that are frequently resumed and long maintained. In such cases, if one can rule out *schizophrenic processes* and *hysterical reactions*, the symptoms are strongly suggestive of the third stage of epidemic encephalitis. I recall a patient shown to me by Dr. Lloyd Briggs the other day at the San Francisco

Hospital, which may be illustrative of this. A young girl, E. A., who has been under observation there for some time, exhibits a very interesting automatism; she repeatedly throws her right upper arm across her face, bending the forearm at an acute angle at the elbow with her nose covered by the bend of the elbow (Fig. 18). There are many symptoms in this patient suggestive of multiple sclerosis, and the age of the patient

Fig. 18.—E. A.—Epidemic encephalitis; the peculiar position of the right upper extremity is frequently assumed and long maintained.

made one think strongly of that malady; but the frequent repetition of this peculiar posture of the upper extremity, the character of the automatic movement, and the persistent uncomfortable attitude must make one consider very seriously, the possibility of the existence of a chronic epidemic encephalitis in her case. Rhythmical movements of the extremities, with retention of the limbs in attitudes that look very uncomfortable should always make one suspicious of chronic epidemic en-

cephalitis. Clonic spasms of the tongue, spasms of the eyelids, and so-called "oculogyric crises" are also very common in chronic encephalitis.

One must, of course, be very careful to differentiate *psychasthenic tics* and *hysterical phenomena* from true encephalitis. Patients who have attacks of marked dyspnea or hyperpnea that are otherwise unexplained, or who suffer from chronic hiccup, from ticlike movements of the face or of the neck or from torsion spasm, should make one think of the possibility of encephalitic infection. I recall particularly one patient, in Baltimore, who had recurring attacks of hyperpnea; in some of her attacks the overventilation was so great that she went into an attack of tetany. The symptoms were at first supposed to be due to hysteria, but a careful analysis of the whole history showed that there had been an earlier acute stage of epidemic encephalitis. This was reported by Dr. Sprunt and myself in 1922.

In view of the fact that the encephalitic virus has a special predilection for the basal ganglia of the brain, in other words, for areas that are supposed to be connected with the affective life and with the impulsive life, it is not surprising that there should sometimes be difficulty in distinguishing syndromes due to chronic encephalitis from the *psychoneuroses* and from other *affective-conative disorders*. Nor should it be forgotten that extrapyramidal motor symptoms and affective-conative symptoms due to encephalitis are more or less accessible to suggestion, though not nearly so markedly as in pure psychoneurotic or psychotic cases. When hysteria is in question, most careful personality studies should be made and one should try to find out whether or not the symptoms could be motivated by some hidden wish of the patient.

Hysterical patients usually show a tendency to dramatization of their symptoms, to the production of theatrical effects, and to attempts at the excitation of sympathy. As Stern points out, in his admirable monograph on epidemic encephalitis, this behavior of the hysterical patient is in marked contrast with the slow-minded indolent behavior or the careless euphoria and true-heartedness of the encephalitic patient with tremor. It is rare that the hysterical patient will tremble for years, or that he will continue to work despite his symptoms until work actually becomes impossible. If, in a patient suspected to be hysterical, one find automatic attitudes, cog wheel phenomena, or passive movements, or persistent extrapyramidal rigidity over long periods, hysteria can almost with certainty be ruled out. Another useful differential symptom, when it is present, is accommodation paralysis, for this symptom is not simulated by psychoneurotic patients.

It should not be forgotten that there are *other forms of encephalitis* that are entirely different diseases from epidemic encephalitis. Among them may be mentioned the encephalitis that follows measles, that which follows scarlet fever, that which follows typhoid fever, and that which

sometimes follows vaccination when too strong a vaccine has been used. During the past year or two there have been many cases of the latter disease in Europe, particularly in Eastern Europe, where a very strong vaccine is employed.

Perhaps the commonest mistake is to confuse *multiple sclerosis* with chronic encephalitis. Involvement of the pyramidal tract is, of course, more common in multiple sclerosis than in chronic encephalitis and yet at least 25 per cent of the encephalitic cases in some epidemics may present pyramidal symptoms. Encephalitis may simulate multiple sclerosis, as it may any other organic disease of the central nervous system. It has been known to give rise to nystagmus, to scanning speech, to loss of abdominal reflexes, to slight disturbances of sensation, and to cerebellar ataxia. Remissions and exacerbations of the symptoms and signs are common both in encephalitis and in multiple sclerosis. A history of the very beginning of the disease is often helpful for differentiation, since an influenza-like infection is more common at the onset of encephalitis than in the early stages of multiple sclerosis, though even multiple sclerosis has been known to manifest its first symptoms after an attack of "grippe." Temporal pallor of the optic disks when present speaks in favor of multiple sclerosis. Delirium and disturbances of sleep in the acute stage are far more common in encephalitis than in multiple sclerosis. The development of extrapyramidal hyperkinetic phenomena is in favor of encephalitis rather than of multiple sclerosis though the intention tremor of multiple sclerosis may be confused with the tremors that develop in chronic encephalitis. Finally, one must not forget that a patient may suffer from both multiple sclerosis and encephalitis. One such case has been observed by Stern clinically and another has been proved postmortem by Neuburger.

Cerebrospinal syphilis may give rise to clinical pictures suggestive of chronic epidemic encephalitis, particularly when, owing to syphilitic disease of the cerebral blood vessels, there has been injury to the globus pallidum. The optic nerves are more often involved in syphilis than in encephalitis. The blood Wassermann, as every one knows, may be negative in cerebrospinal lues, though the Wassermann reaction in the spinal fluid is usually positive and there are other findings in the fluid that speak for cerebrospinal lues. I have seen cases of chronic epidemic encephalitis that manifested a *tabes-like syndrome*, and confusion even with *dementia paralytica* has been reported in the literature.

Tumor of the brain should also be ruled out before a positive diagnosis of chronic epidemic encephalitis is made. It has long been known that drowsiness, Parkinson-like phenomena, or cerebellar symptoms, may occur with tumor of the brain and may give rise to the suspicion of an encephalitis. In several such cases, tumors of the basal ganglia, tumors in the region of the third ventricle, tumors of the pons, and tumors of the hypothalamus have been found at autopsy. On the other hand, the

diagnosis of tumor of the brain, particularly tumor of the cerebellum, has sometimes been made when at operation no tumor was found and subsequent examination at autopsy proved that the disease was really epidemic encephalitis. Where there is real doubt, the making of ventriculograms after air injection by Dandy's method, may be decisive.

On going around the wards the other day Dr. Gerstle spoke of the possibility of confusion of epidemic encephalitis with *Schilder's periaxial encephalitis*. There are, it is true, cases reported in the literature of confusion of the two diseases. I have not yet seen a case that I felt sure was Schilder's periaxial encephalitis, but I shall be on the lookout for one.

My own experience in diagnosis makes me very wary of being dogmatic about the existence of epidemic encephalitis in cases in which the syndromes are atypical. There are so many possible sources of error that even those of us with large experience in the study of encephalitis cannot be too careful in the avoidance of unjustifiable diagnosis of this disease. When we are in doubt, it is better to be temporarily satisfied with a diagnosis of "organic encephalopathy" with mention, as far as possible, of the localization of the lesions, leaving a decision as to the exact nature of the malady open.

With reference to the differentiation of a Parkinson-like stage of chronic epidemic encephalitis from true Parkinson's disease, a few more words are in order. The question does not come up in cases in which the Parkinson-like symptoms have developed directly out of an acute or out of a pseudoneurastheniform stage of encephalitis. It is more likely to come up in cases in which an acute stage is absent from the patient's history. Even then the occurrence of Parkinson-like symptoms in a young person speaks for epidemic encephalitis rather than for true Parkinson's disease.

The tremor of true Parkinson's disease, is as I have said, somewhat different, as a rule, from that of the parkinsonian stage of encephalitis, and yet it may be impossible to distinguish the two diseases by the tremor alone. The typical pill-rolling tremor is rarely present in epidemic encephalitis and yet we have seen that it did exist in one of our patients today, a man who undoubtedly had encephalitis preceding his parkinsonian state.

In true Parkinson's disease (paralysis agitans) it is rare to find as much involvement of the head, the neck and the muscles of mastication as in encephalitis. In true paralysis agitans, too, hypochondriacal moods are more common than in myastatic encephalitis, as are also the phenomona of senile dementia. Moreover, the rigidity and tremor develop much more slowly, as a rule, in true paralysis agitans than in the cases of chronic epidemic encephalitis.

I have seen a few cases in which a Parkinson-like syndrome developed during the acute stage of encephalitis. In my experience, these cases are

much more favorable as regards recovery from the Parkinson-like symptoms than are the cases in which the parkinsonian syndrome does not devlop until the third stage of the disease has been reached.

TREATMENT OF CHRONIC EPIDEMIC ENCEPHALITIS

We possess no specific treatment for this disease and yet we can do much to ameliorate the pitiable condition of these patients. In the milder cases, it is sometimes possible to arrest the progress of the disease even in the parkinsonian stage, though it is rare to see the parkinsonian syndrome pass off altogether, if, indeed, this ever occurs outside of the acute stage. In the severer forms of chronic encephalitis with parkinsonism, there is slow progression in spite of all forms of treatment, but much symptomatic relief can be given and the patient should never be neglected despite the limitations of our therapy.

Very considerable relief can be given to the rigidity and the tremor by the administration of hyoscine hydrobromide. Formerly, we began with small doses, 1/400 or 1/200 grain, but thanks to the experience of one of my colleagues, Dr. L. B. Hohman, we have learned that we can give much larger doses with safety and with very great benefit to the patients. In some cases we have given as much as 1/50 grain three times a day over a considerable period. One has to keep in mind the possibility of the development of a hyoscine delirium, though I have never yet encountered it in one of these cases. Should such delirium appear, the administration of the drug should be stopped, at least for a time. I have recently seen great relief of pathologic drowsiness in chronic encephalitis follow upon the administration of hyoscine in full doses.

Sometimes the combination of atropine with scopolamine does more for the tremor than will either drug alone. On account of the chronicity of the process, it is best to give the drugs by mouth, rather than to make use of hypodermic injections. An occasional course of cacodylate of soda may be given hypodermically and sometimes with benefit, particularly if the patients be undernourished. For about five years stramonium has been used for the parkinsonian syndromes by the method of Juster. In Seattle satisfactory results have been obtained with it by Dr. Epplen, and Dr. Garnett Cheney tells me that the reults in some 30 cases treated here in San Francisco have been quite encouraging.

In patients who exhibit troublesome muscular spasms, barbital with amidopyrin may be given, say ½ Gm. of each, repeated as often as necessary. Morphine is best avoided altogether in these chronic cases. Recently, the use of harmine (banisterine) has been recommended for chronic epidemic encephalitis; as yet I have had no experience with it.

Systematic psychotherapy and reeducation of the patient to the performance of movements that have been restricted by the rigidity I consider to be very important. These patients tend to make far fewer movements than they are capable of making. They have a *distinct*

disinclination for muscular movement and they should be urged to overcome it. It is often surprising how much one can do by systematic encouragement of the patients to increased exertion.

General massage is useful, but not too much is to be expected of it; nor have I seen any especial benefit from the application of electricity in treatment.

Not much is to be expected either from the use of convalescent serum in the late stages of chronic encephalitis, though I think it should be tried (when it is available) in acute stages of the disease.

Foreign protein therapy has been tried in this disease, as in so many chronic diseases of the nervous system, with approximately similar effects. Treatment by inoculation with malaria is also being tried out, because of the favorable effects produced in dementia paralytica, but more experience with it is required before a definite statement regarding its efficacy can be made.

Where there is much drooling because of excessive sialorrhea atropine is the best remedy. In very severe sialorrhea one may lessen the parotid secretion by *x*-ray therapy or by applying radium.

The great increase in the number of chronic encephalitic cases promises a future full of difficulties from the sociological standpoint. Many of these patients are entirely without means and the homes for incurables are likely soon to be overcrowded with sufferers from this malady. It is possible that special encephalitic stations will have to be established for the care of such patients.

PATHOLOGIC ANATOMICAL CHANGES IN CHRONIC ENCEPHALITIS

The pathologic anatomical changes found in cases of death from encephalitis have been most interesting to pathologists and histologists.

To the *naked eye* the central nervous system may look wholly normal and a pathologist on hasty examination might assume that no pathologic lesions were present. In some instances, it is true, there is a little edema of the brain and, perhaps, a slightly increased vascularity in patients who have died during the acute stage of the disease; but there are no large hemorrhages such as are met with in the focal hemorrhagic encephalitis of influenzal origin. Epidemic encephalitis is essentially a nonhemorrhagic disease of the brain; if any hemorrhages at all are found, they are minute. In patients dying during the chronic stage of the disease the only changes visible to the naked eye may be those of atrophy, particularly in the region of the frontal lobes, the substantia nigra, the globus pallidum, and the putamen; but, in many cases, this atrophy may be so slight as to escape the observation of the man who makes the autopsy.

It is on *microscopical examination* that the characteristic features of the pathologic changes in epidemic encephalitis come into view. Though we speak of encephalitis, the inflammation present differs from ordinary

inflammations in that there may be little, if any, inflammatory exudate with emigration of polymorphonuclear leukocytes into the tissues. On the contrary, we have to deal with an infiltrative, proliferative, and alterative process, these changes being much more pronounced than the exudative phenomena.

In the walls of the blood vessels and near them you may meet, at the sites of predilection, aggregations of lymphocytes, plasma cells, polyblasts, and macrophages. It has been assumed that most, if not all, of these arise from the connective tissue elements of the vessel walls. The macrophages come from glia cells; even the small mononuclear elements in these infiltrations are predominantly found in the intra-advential and periadventitial space (Virchow-Robin space). Possibly some of the small mononuclear elements are of hemic origin.

The alterations in the nerve cells, themselves, during the acute stage of the malady, consist of acute swelling or homogenization of the tigroid substance and, in severer cases, of liquefaction of the cells. Signs of lipoid degeneration can also be made out. There may be a marked reaction upon the part of the glia tissue and the new cells formed may contribute to the appearance of focal infiltration by their addition to the products of perivascular connective tissue activity.

These histologic changes in the central nervous system show an astonishing distribution, since there is a marked predilection for certain special sites. First, it is the gray matter rather than the white matter that is predominantly involved. In the second place, it is the gray matter of the brain stem and the gray masses of the diencephalon that are chiefly affected, whereas the gray cortex of the brain, the gray matter of the spinal cord, and that of the cerebellum are relatively less often involved.

In many cases most of the changes are localized in the gray matter around the third ventricle and along the aqueduct of Sylvius. Changes are also very common in the walls of the fourth ventricle, in the tegmentum of the cerebral peduncles and of the pons, as well as in the thalamus and the hypothalamus.

In patients dying during the chronic stages of myastatic encephalitis there may still be areas of infiltration similar to those seen in the acute stage, but, usually, there are only a few such areas, and they are minimal in size and extent. In some cases no areas of infiltration at all can be seen in the chronic stages. Histologically, however, atrophic changes can be made out—sometimes in the corpus striatum (pallidum and putamen), very often in the substantia nigra and also in the frontal regions of the brain.

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COLLAPSE OF A PATIENT AFTER A TWELVE-HOUR WALK FOLLOWED BY TONIC CONVULSIVE SEIZURES AND SENSORY DISTURBANCES; TENTATIVE DIAGNOSES OF STRYCHNINE POISONING, TETANUS, AND HYSTERIA; POSSIBILITY OF EPIDEMIC ENCEPHALITIS[1]

THE man before you has recently passed through an extraordinary experience, and the symptoms he has presented have been the cause of considerable perplexity as regards diagnosis. After you listen to an account of the development of his symptoms I should like to discuss the findings with particular reference to the diagnosis.

CASE HISTORY (SUMMARIZED BY DR. PAUL MICHAELS)

The patient, Edward C., a white vagrant, forty-two years of age, was brought in the police ambulance to the hospital on November 24, 1929. He was apparently unconscious on admission but soon regained consciousness. A general physical examination was made, and, on testing for the Babinski reaction, the patient had a tonic convulsive seizure with opisthotonos, gave a loud cry, and manifested rather bizarre symptoms. The convulsive seizure was somewhat suggestive of strychnine poisoning, or of tetany.

It was subsequently learned that he was of German descent and unmarried. He had always lived a vagabond existence, working at odd jobs. He had but little schooling, never having finished the grammar grades. After many years of dissipation, he became a devout Salvation Army follower and his habits now regarding alcohol and tobacco are exemplary.

Family History.—One brother is said to be living in Oakland, though where and under what conditions could not be discovered. Nothing else could be found out about the family.

Past History.—He had the ordinary childhood diseases and his appendix was removed thirteen years ago. One finger was amputated following cellulitis two years ago.

In the generalized convulsion that followed the Babinski test made here, the body assumed the attitude of opisthotonos; the arms, legs, hands, and fingers were held rigidly in slight flexion. The face showed a series of grimaces. Apparently the patient had severe pain, for he cried out. The whole affair struck us as sensational and was bizarre in nature. Though he was able to talk throughout the seizure, his voice was halting.

On **physical examination,** the temperature was 101 F. and the pulse rate 138. The bloodppressure was 130 systolic, 70 diastolic. The eye muscles and eyegrounds were negative. The deep reflexes were hyperactive. The pharynx was reddened.

He continued to have tonic spasms about every ten minutes though they grew gradually less severe.

After the patient had sufficiently recovered, he told us that he had undertaken to walk to Oakland from Marysville (about 140 miles), starting at about 8 o'clock in the morning. At 4 in the afternoon he became exceedingly weak, and he collapsed upon the road, becoming unconscious. On recovery, he was picked up by a passing motorist and brought to Oakland. On the following morning he had a similar attack upon the

[1] Clinic before the Alameda County Medical Society, December 16, 1929.

street in Oakland and was brought in the police ambulance, as stated, to the hospital. On the night of admission he developed a spastic paralysis of the upper and the lower extremity (on the left side). He exhibited a painful reaction on passive motion, but there was no evidence of pathologic reflexes. Sensation was slightly impaired, but in nerve root rather than peripheral nerve distribution. Later on this anesthesia disappeared, except for an area over the right buttock.

Course in the Hospital.—At no time could the presence of any pathologic reflexes be demonstrated. The areas of anesthesia gradually changed. Thus the band of anesthesia above the waist disappeared entirely as did the anesthesia on the soles of the feet and heels. The only anesthetic area remaining was over the right buttock. His pains have been transitory and they have changed in location and have not corresponded to the distribution of any peripheral nerve.

He complained of cramplike pains across the abdomen on both sides, the distribution corresponding to the tenth or the eleventh thoracic nerves. On December 6th, these pains were limited to the left side of the abdomen and were cramplike in nature. On December 12th he complained of pain over the left buttock and in the left axilla. He made the following statement: "God has willed these spasms and tells me to have them. I am safe in his hands and have no fear."

Laboratory Examination.—*Blood.*—Red blood cells, 4,050,000; hemoglobin, 77 per cent; white blood cells 11,850; differential count, polymorphonuclear neutrophils, 90 per cent; small mononuclears, 10 per cent. Wassermann negative. Serum calcium 10.6 mg. per 100 cc. CO_2 combining power 67.

Urine.—Negative.

Cerebrospinal Fluid.—Under normal pressure; no cells seen. Very faint trace of globulin, colloidal gold negative, Wassermann negative.

x-Ray examinations of the skull and spine were negative.

Treatment.—Though the spasms resembled those of strychnine poisoning, no history of such intoxication could be obtained. Because evidence of a small cutaneous wound was discovered, and in view of the occurrence of tonic spasms, he was given 20,000 units of tetanus antitoxin. Sedatives were administered, first to control the convulsions and, later, to allay the patient's apprehension.

Psychiatric Examination (Dr. R. L. Richards).—The patient states that he was never successful at school and that he was taken out at eleven years by his father. His brother was "bright" and finished high school. He becomes very emotional in describing his mother's attitude toward his mental deficiency. At thirteen years of age, he became a farm hand and has remained so since then. He wandered from Pennsylvania to Indiana, to Michigan, and to Illinois. Once he did some "paint-dipping" (for two years) but he did not like that work. His father died in 1913 and his mother in 1927. He is very proud of having helped his mother. In 1910 (at the age of twenty-one years) he was "converted," and repented his former drinking, gambling, etc. He has been a devoted adherent to the Salvation Army since then. After the death of his mother he worked his way West to find his brother. He had understood that his brother was in Oakland, but he has never found him. He can read, but he spells poorly and he says he never could write well enough to write letters. Apparently he has tried to compensate by the practice of virtue for what he lacked mentally. Mental level ten years; Binet Simon I. Q., 63 per cent. He has complained of recurrent headache and stomach trouble. Last summer he had his teeth pulled out because a doctor in Sacramento said it would "cure his stomach trouble."

He had left Marysville to try to reach his brother and he arrived at Oakland, he thought, with $43 in his pocket. He had made his way selling "stick candy" in the streets and he thought he could continue making a living in that way. His mother had liked the brother better than she liked him.

After walking from 8 A. M. to 4 P. M. he felt dizzy, nauseated, and sick. "Things went black" and he fainted. He did not think of his pocketbook, when a man picked him up. During the ride to Oakland (or vicinity) with a stranger, he was more or

less confused. Next morning when he tried to pay for breakfast, he found that his money was gone; then followed the hysterical episodes described in the history. Today (December 14th) he is still emotional and cries on slight provocation.

He shows well-defined narrowing of the fields of vision and convergent weakness of the eyes. Fine tremor is not marked. Reflexes are equal but exaggerated. On testing responses to light touch, there appears to be slight anesthesia, but this varies from time to time, is not very marked, and conforms to no nerve distribution. In the examiner's opinion we have to deal with:

1. Probable hysteria.
2. Moron, I. Q., 63 per cent (estimated).

DISCUSSION OF THE CLINICAL DATA ACCUMULATED

This is a truly remarkable history and the diagnostic problem is not altogether easy of solution. Let us consider separately some of the more important features of the case.

The Fever and Leukocytosis.—This man's temperature was 101 F. on admission. He had a leukocytosis of a little over 11,000 white cells, with a relatively high percentage of polymorphonuclear neutrophils, suggestive of some acute infection. It was noticed that his pharynx was reddened and it is possible that an upper respiratory infection, perhaps of influenzal type, could account for the fever and the leukocytosis. The excessive fatigue of the long walk might possibly have contributed also to these findings. I think, however, that we must admit that the fever and leukocytosis point to some real organic process of an infectious nature.

The Collapse Upon the Road.—This patient, after many hours of walking, suddenly felt weak, "things went black" in front of him, and he fell in a faint on the road, where he was found unconscious. This might have been a fatigue phenomenon, or, when we consider the fever and leukocytosis, it might have been related to an infectious process. The possibility of a localization of the infectious process within the central nervous system naturally comes to mind.

The Convulsive Seizures with Tonic Spasm.—On testing for the Babinski reaction, Dr. Michaels was surprised to see the patient go into tonic spasm with opisthotonos and rigidity of the extremities, but with slight flexion. Such convulsive seizures were repeated every ten minutes or so, though with decreasing severity. Later on, there were cramplike pains in the lower abdomen, suggestive of cramps of the abdominal muscles, or of cramplike contraction of the intestines. These tonic spasms were thought to be those of strychnine poisoning or possibly of tetanus. As no history of strychnine poisoning could be obtained and as there was a slight wound of the skin, tetanus antitoxin, in large doses, was administered.

What was the nature and origin of these tonic spasms? From the standpoint of localization, one cannot help but think of the phenomena as resembling those of decerebrate rigidity, which, as you know, are

somewhat different in man from those observed in animals. Such phenomena of decerebrate rigidity are usually dependent upon the cutting off of cerebral influences of inhibition upon the lower reflex centers, so that a pronounced hypertonus is maintained by Deiters' nucleus. If there were such a release of the lower centers from the inhibition of the higher centers it must have been a transitory release, for the rigidity has passed off, though there is still a little hyperactivity of the reflexes. One might think of some toxic process involving the midbrain or the cerebral peduncular region, or one could, I suppose, think of an hysterical mechanism, which often makes use of definitely systematized motor mechanisms of the central nervous system.

The Sensory Disturbances.—Sensory disturbances of two sorts were observed in this patient. First, there were severe pains accompanying the tonic spasm of the musculature, and, later, there were spontaneous pains that were not of neural distribution, though they were confined to the left side of the body, left buttock, left abdomen, and left axilla. In this connection, it is interesting that the statement is made that, on the night after admission, he exhibited a temporary spastic paralysis of the arm and leg on the left side.

The second disturbance of sensation was cutaneous anesthesia (or hypesthesia) in certain definite domains. Thus, at first, the anesthesia corresponded to the radicular distribution of T_{10} and T_{11}, as well as of the second sacral segment. Later, this anesthesia largely disappeared, though a little remained over the left abdomen (region of T_{10} and T_{11}). This also disappeared later, leaving only an area of anesthesia of circular shape over the left buttock.

It seems to me that these sensory disturbances are of real diagnostic importance. It would be very unusual for hysterical anesthesia to assume such segmental distribution (corresponding to the tenth and eleventh thoracic segments and the second sacral segment). The pains on the left side of the body, though not in distributions corresponding to nerves or segments, could very well be so-called "central pains." This idea is reinforced by the fact that a spastic paralysis of the left upper extremity and the left lower extremity (of temporary duration) was observed.

The **cerebrospinal fluid** was negative, except for a trace of globulin, but this is not entirely negative. A trace of globulin is suggestive of an organic process.

The Mental Deficiency.—The whole history of this patient, including his inability to do school work, to learn to write, and to take care of himself from the economic standpoint, indicate a high grade of mental deficiency or "oligophrenia." The naïveté of his religious reactions also points in the same direction. Moreover, Dr. Richards found by the Binet-Simon test that he corresponds in mentality to the mental age of ten; in other words, he is a moron.

DIFFERENTIAL DIAGNOSIS

Strychnine poisoning seems to be ruled out by the history. Moreover, the symptoms of strychnine poisoning set in, as you know, very quickly after absorption of the alkaloid. If he had taken strychnine before setting out on his walk, he would have had these tonic spasms in the early forenoon. It is not probable that he could buy strychnine during his march.

The fact that very slight stimulation of the skin precipitated the tonic spasm was certainly suggestive of a strychnine phenomenon, for the tetanus-like attacks in patients with strychnine poisoning usually start suddenly after the application of some external stimulus. Sometimes a slight noise or slight shaking of the bed, or even a strong light stimulus will precipitate a seizure and opisthotonos will appear; usually there is respiratory standstill and the patient suffers terrific pain. The attacks tend to recur every few minutes. The pulse is usually slow during the attacks. You will remember that this man's pulse rate was 138 on admission.

It would have been possible to make sure about strychnine poisoning by examination of the urine. If one extract the urine with chloroform, the alkaloid can easily be isolated, and injection into a frog or into a mouse will produce a typical tetaniform attack in the animal, as only 1/30 mg. is necessary for this in a frog and only about $\frac{1}{2}$ mg. for the mouse.

In the absence of strychnine poisoning other things that resemble it have to be thought of, among them tetanus, hydrophobia, hysteria, hystero-epilepsy, and organic diseases involving the brain stem, with cutting off of inhibition from the upper centers.

Since a small wound was found upon the skin and since the tonic spasms were suggestive, I think that the hospital physicians were quite right in administering a dose of tetanus antitoxin. Subsequent history, however, lends but little credence to the suggestion that the man has tetanus.

Rabies is also ruled out by the absence of any history of a bite by a mad animal.

Hysteria should, of course, be seriously thought of as possibly accounting for the nervous and psychic phenomena. Here is a mentally deficient man who gives a history that would fit very well into the development of a hysterical mental mechanism. He was away from his family; and, though he had $43 in his pocket, he decided to walk all the way from Marysville to Oakland, a distance of some 140 miles. Under the influences of fatigue and of some mild pharyngeal infection, he collapsed, and afterward exhibited motor and sensory manifestations that could easily lead to the idea of an hysterical episode. As a rule, however, the cerebral fits of hysteria consist chiefly of expressive movements or of muscular contractions that correspond to those that accompany strong emotions of various sorts, such as anger, irritation, joy, pain, and the

like. Sometimes the movements reproduce those of some earlier experience, such as an assault, an accident, or a fight. Often there are hysterical hypesthesias along with the development of hyperesthesias over the body. Sometimes there are definite anesthesias.

In major hysterical attacks, the patients sink down, as a rule, and assume and maintain for some time remarkable attitudes (such as the arc of a circle) or various pathetic or theatrical positions, or they may exhibit wild rotating movements. In such attacks the patients do not injure themselves, they never bite the tongue, and the attacks are not followed by a postconvulsive sleep.

Hysterical anesthesias usually affect one extremity, or one half of the body, or two extremities simultaneously. Instead of following a segmental distribution, the localized anesthesia in hysterical patients usually corresponds to areas of skin covered by certain articles of clothing, such as gloves, drawers, stockings, or chemise. In some hysterical patients, the condition known as akinesia algera develops; in this there is immobility on account of pain, although no cause for the pain is discoverable. Interesting as the hypothesis is that hysteria may account for the peculiar behavior of this patient, particularly in view of the mental mechanism that Dr. Richards disclosed, I should be very cautious before deciding that we are, in reality, dealing with hysteria. On account of the fever, the leukocytosis, the character and distribution of the tonic spasms, and, especially, the segmental distribution of the sensory disturbances, I am inclined to think that we have had to deal, and are dealing, with an organic disease of the central nervous system, possibly with an infectious inflammatory disease. The possibility of an atypical form of epidemic encephalitis comes into my mind. Not infrequently this begins with an influenza-like attack and is associated with hyperkinetic phenomena, though the commoner forms of hyperkinesis in epidemic encephalitis are of the myoclonic and the choreatic types of disturbance of motility. Still, hyperkinetic attacks resembling decerebrate rigidity have been observed in epidemic encephalitis. Moreover, as you know, the virus of encephalitis shows a predeliction for the midbrain and the basal ganglia, regions in which a transitory lesion might release a temporary decerebrate rigidity. Moreover, there would seem to be multiple lesions in this patient, even though the symptoms have been transitory. I think that the gray matter in the region of the tenth and the eleventh thoracic segments and the gray matter in the region of the second sacral segment must have been at least temporarily injured. The central pains in different areas could also be due to a patchy edema of different parts of the gray matter of the spinal cord. As you know, in the acute stage of epidemic encephalitis, nothing is more common than to see fleeting symptoms, either motor or sensory. Eye-muscle paralyses come and go, pains come and go, anesthesias appear and disappear, as do also the hyperkinetic disturbances.

We shall all be very much interested in following the further course of the malady in this patient. He has had no pathologic drowsiness, as far as I can learn. It will be interesting to see whether or not any eye-muscle paralyses develop, or any myoclonic twitchings anywhere in the body. Above all, it will be important to know what happens to this man months or years from now, for if he should develop a Parkinson-like syndrome later on, the diagnosis of epidemic encephalitis would be made certain.

DIAGNOSTIC CONCLUSIONS

For the present, we must, I think, be content with the following diagnoses:

1. Disseminated encephalomyelopathy (probably organic), with attacks of generalized tonic spasms simulating tetanus, strychnine poisoning, or decerebrate rigidity, with attacks of painful cramps of the abdominal muscles, with areas of pain suggestive of a central origin, and with transient anesthesias of segmental distribution (T_{10}–T_{12}; S_2), and with slight increase of globulin in the cerebrospinal fluid (possibility of atypical epidemic encephalitis to be kept in mind).
2. Secondary anemia (hemoglobin 77 per cent).
3. Oligophrenia (moron), with the mental age of ten years and a history of illiteracy and vagabondism.
4. Undernutrition (13 pounds).

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DISCUSSION OF THE NATURE OF THE AFFECTIVE DISORDER IN A PATIENT WHO HAS HAD MANY MAJOR AND MINOR OPERATIONS AND IS AT PRESENT CONSIDERING THE ADVISABILITY OF A FURTHER MAJOR OPERATION IN THE HOPE OF GAINING RELIEF FROM SYMPTOMS[1]

A FEW days ago Prof. Kerr, when mentioning various cases that might be suitable for presentation at this amphitheater clinic, stated that possibly I might be interested in discussing with you a patient who has had a large number of surgical operations and who now expects to undergo still another serious operation in the hope of securing relief from her symptoms. I at once said that the history seemed to me to be somewhat suggestive of an abnormal mental state, inasmuch as a surgical history of this sort is very common among mild psychopaths, and I thought that I should enjoy presenting such a case to the class.

The clinical history has been summarized and has been placed at my disposal by Dr. Wm. L. Bender.

The patient, Mrs. William H., a married white woman, age forty-one years, had been referred to Dr. Bender for study by a physician in another State.

The **chief complaints** when she came to San Francisco on March 26, 1929, were of weakness, hemorrhoids, and pain in the pelvis and rectum.

Family History.—The father died at sixty-six of cancer of the stomach, the mother at sixty of pneumonia. One brother died of pneumonia and two sisters were accidentally drowned. The patient has had six half-brothers and half-sisters; four of whom are well, one was born dead, and one died of tuberculosis. The patient is of Russian-Jewish extraction on both sides. She is said to be happily married and to have borne three children, all of whom are well.

Past History.—The patient had scarlet fever in early childhood and several other infections common in childhood. At twenty-eight, after a left-sided pneumonia, an empyema developed, which was operated upon with resection of a rib and drainage, followed by recovery. In 1928 she suffered from a mild influenza of one week's duration. A chronic appendix was removed at eighteen, the operation relieving a frequently recurring nausea.

Last year she underwent a thyroidectomy. Two months later the tonsils were removed and many teeth were said to be infected and were extracted.

Eleven months ago the gallbladder was removed and it is said that it was found "badly diseased," although there were no gallstones. Last April her uterus was operated upon by dilatation and curettage and a repair of the cervix and perineum was made at the same time. An operation for hemorrhoids was also performed and the anal sphincter was stretched. During the present month, on cystoscopical examination and pyelography, she was found to have polyps and a papilloma of the bladder. Fulguration was done. The pyelographic study indicated that there were some kinkings of the ureter on the right side with mild hydronephrosis on that side and physical

[1] Amphitheater Clinic at the University of California Medical School, November 27, 1929.

examination revealed a somewhat loose kidney on the right. As the patient has abdominal pain she is at present considering the advisability of having the right kidney operated upon in the hope that she may be relieved of this pain.

Recently, the menstrual periods have been becoming more scanty and somewhat painful; they are associated with constant feeling of oncoming period, especially on arising in the morning.

Her habits, aside from the frequent resort to surgery for relief of symptoms, have been good, except for possible over-indulgence in coffee.

Present Illness.—Although the patient has laid emphasis on her somatic complaints and has repeatedly sought relief by urging medical and surgical therapy for one or another part of her body, it was found on close inquiry that her health during adult life had been reasonably good until about three years ago when, after one year of great strain because of much sickness in her family, she began to have a good deal of trouble with her teeth. After consulting a dentist three abscessed teeth were extracted, but the dentist told her that he felt that she very much needed the services of a physician in addition to those of a dentist. The dentist had evidently observed an abnormal nervous and mental state. One week after this conference with the dentist she had what she calls a "nervous breakdown" as a result of which she remained in bed several months, feeling very weak, being sleepless, and suffering from palpitation of the heart. She lost some 10 pounds in weight during this period and she states that she was constantly weeping. About the same time she began to have attacks of "cramps" in the epigastrium, which recurred frequently, over a period of several weeks; they were not accompanied by nausea, vomiting or jaundice. One physician considered these symptoms as being due to goiter and, on study of her case, told her that her basal metabolism was very high, that there was no acid in her stomach contents and that the *x*-rays revealed mild gallbladder trouble.

After a few months a thyroidectomy was performed and the patient states that the palpitation thereafter lessened, though the symptoms otherwise were not improved and she continued to spend much of her time in bed.

Two months after the thyroidectomy, a tonsillectomy was performed; she states that she had no symptoms referable to the throat, but that the surgeon found that her tonsils were "badly diseased."

About two months after this, her remaining teeth were extracted, apparently because the pulps were dead, though there seems to have been no other evidence of infection of these teeth.

For the gnawing, cramping sensation in the midabdomen she took HCl intermittently. She states that she continued to have from two to three attacks weekly of severe pain in the right upper quadrant and that, at this time, there was a little fever, which her physician thought might be due to mild infection of the gallbladder. Because of continued pain in the abdomen and a further loss of weight the gallbladder was removed.

During convalescence from the gallbladder operation, she had what she described as a "severe heart attack with knifelike pains about the chest, front, and back," associated with dyspnea lasting for three hours, for which a sedative suppository was given. After this she had mild recurrences of the same chest pains and noticed their onset after the swallowing of various medicaments, such as aspirin, codeine, and glandular mixtures. She found that the only medicine she could take without producing attacks were a few drops of digitalis and the diluted HCl.

Recently, she has averaged one attack of chest pain per week, even when she took no medicine except those last mentioned; the attacks have occurred independent of exertion or other apparent cause. In some instances the attacks of pain in the chest have started with epigastric cramps, but they have not been associated with a feeling of gas in the abdomen or of pressure upward from the abdomen. She has continued to have also the "crampy" abdominal attacks, sometimes accompanied by a feeling of a "lump under the breastbone" and heartburn.

But the complaints thus far mentioned do not by any means complete her list. For she states that she has suffered from hemorrhoids ever since she had children. She also states she has been subject to headaches since childhood; they have been usually one sided and accompanied by nausea. She has grown progressively weaker and, during the past few months, her general condition has gradually grown worse. The symptoms of palpitation, nervousness, fatiguability, weeping, and depression have all become exaggerated.

On **physical examination** the positive findings included undernutrition, retraction of the thorax after operation for empyema with pleural adhesions and right nephroptosis with slight right hydronephrosis. There was some deviation of the nasal septum to the left with congestion of the mucosa over the turbinated bones. The pulse rate is 84, the blood pressure 104/76. The liver edge has been palpable 2 to 3 finger breadths below the costal margin. The spleen is not palpable. All the reflexes are normal.

Laboratory Examinations.—*Blood.*—Red blood cells, 4,130,000; hemoglobin, 68 per cent; color index, 0.7; white blood cells, 8400; differential count, polymorphonuclear neutrophil leukocytes, 79; small mononuclears, 15; eosinophils, 2; transitionals, 4; no anisocytosis or poikilocytosis. Platelet count normal. Wassermann negative.

Stomach contents contain no free HCl; combined acid only 4 acidity per cent. Rennin and pepsin absent. Occult blood negative.

Urine.—Negative.

Stool.—Negative for ova and parasites; no occult blood.

x-Ray examinations have been negative except for evidences of spastic colon.

An **electrocardiogram,** on one occasion, showed a sinus bradycardia; the heart rate was 43, with respiratory arrythmia and left ventricular preponderance.

To Dr. Bender, the patient continued to complain much of her symptoms and of her depression, often in a rather whining voice.

On October 28, 1929 she entered the University of California Hospital for further study, in the hope of finding the basis for the "severe cramps" from which she suffers. She then described two types of painful attacks. In one type the attack begins with a gnawing sensation in the region of the umbilicus, soon becomes cramplike and rises into the upper abdomen in the midline, after which it radiates to both sides, extending around to the lumbar region. This pain causes her "to double up and to press upon the abdomen." The application of heat to the abdomen gives some relief to these pains after three or four hours. Emetics formerly relieved these pains but, recently, they have aggravated the cramps. She asserts that the pains do not let up fully until at least twelve hours have elapsed and afterward there is a residual soreness that continues for several days. These attacks recur approximately once a week and stand in no relation to food intake. They have occurred more frequently in the morning, but the pains grow worse toward evening.

The second type of pain from which she suffers she designates as a "painful heart attack." This pain still follows any type of medication. She describes it as a viselike pain, which grips her between the upper midabdomen and the back and gives her a sensation as though a light cord were tied around her lower chest. With it there is a sensation of a lump beneath the breastbone, which makes it difficult for her to take a deep breath and she has also a burning sensation in her throat.

She asserts that neither of these two types of pain resembles in any way the attacks of pain from which she suffered in the right upper quadrant before her gallbladder was removed.

With the aid of petrolagar she has regulated her bowel movements, but the stools are said still to be small and to be pencil shaped. She has not noticed the presence of blood or of mucus in her stools.

Psychiatric Report (Dr. E. C. Read).—The patient was the youngest in a family of seven; she was seven years younger than the next older child. Her mother was near the menopause when patient was born. The patient was the family "pet" and her brothers and sisters have always taken a paternal and maternal interest in her:

they are still helping to finance her in her numerous illnesses. This patient is of Russian-Jewish parentage and is prone to translate her continual depression into physical pain and discomfort. She recites a long history of illnesses and operations extending over the past twenty-five years. She also tells of numerous illnesses, operations and misfortunes in the family. Her husband has been a disappointment—a failure as a provider; he is at present earning only $18 a week. The patient naïvely remarks: "If I were well enough I would go to work myself and earn some money." She states that she "weeps for days at a time" and for the past three years she has been taking from 40 to 70 grains of bromide daily. Though originally ambitious she asserts that she has been thwarted and emotionally overcome by a series of unfortunate circumstances.

Conclusion.—Though the patient could scarcely be normal mentally or physically after the numerous operations she has undergone and the amount of drugs she has consumed, she evidently has a marked neurotic tendency, which has been fostered by circumstances and by treatment.

DISCUSSION OF THE CLINICAL FINDINGS

The somatic abnormalities still present include (1) moderate undernutrition; (2) achylia gastrica with postoperative abdominal adhesions and spastic colon; (3) right nephroptosis with slight right hydronephrosis, but without impairment of renal function; (4) retraction of the thorax after empyema, and old pleural adhesions; in addition, there has been evidence of (5) migraine, of (6) a vagotonic tendency, of (7) the onset of menopause and of (8) a secondary anemia of moderate grade.

But what I am very much interested in, also, is the *mental state* of this patient and particularly the *affective disorder* that she exhibits.

The multiple surgical episodes through which she has passed, together with the further surgical operation that she has contemplated, would seem to afford some reason for the existence of at least a "reactive" depression. I am wondering, however, if we may not be dealing here, in reality, with a primary depression—the depressive phase of an elative-depressive psychosis.

I have been talking to the patient this morning and I find that her feelings of sadness and gloom have already lasted a long time—more than two and a half years. During this time, she has had difficulty in concentrating and in making decisions, she has tired very easily, and everything has been an effort to her. She has lost many of her former interests and cannot understand why, except that she has had to be operated upon so very often. She says definitely that her thoughts come more slowly than they formerly did and that even her movements have been slowed up. She has had many weeping spells; indeed, she wept as I talked with her. She admits that she has a kind of "internal torture" that is harder for her to bear than physical pain, but she has been turning to operation after operation in the hope that she may get relief, not only from local symptoms, but from the general torture that she suffers. She blames herself rather than anyone else for yielding to these feelings of depression, but, on more closely questioning her, I find that she knows

that she cannot help the condition and that her common sense tells her that she really ought not to blame herself for its existence.

On account of the many illnesses she has passed through, I made inquiry as to the existence of hypochondriacal ideas. She undoubtedly harbors many ideas associated with local maladies of organs or organ systems and she definitely tries to interpret her feelings of melancholy into terms of organic physical disease. In other words, she presents the picture commonly known as that of a *chronic invalid reaction.* She has not objected to any of the surgical procedures that have been recommended to her, but has rather welcomed them, since they held out, in her mind, promise of relief from her torture. And now she really would like to have the further operation through which the kidney would be stitched into place; she does not at all shrink from it, but, on the contrary, I gained the impression that she rather rejoices in the possibility of its performance. Some of us write too many articles and may be said to suffer from *cacoethes scribendi*, or the itch to write; some surgeons are said to have an itch to cut, or so-called *cacoethes secandi.* Yesterday I was talking with your dean as to the proper term to designate one who has the urge to be operated upon and he suggests that we speak of *cacoethes scalpendi.* I suspect that each of these forms of pruritus may be accessible to therapy only with great difficulty!

I look upon the hypochondriacal ideas of this patient as a pathoplastic coloring of a primary depression. I could elicit no ideas of reference or any definitely paranoid ideas. The patient certainly does not belong in the group that we designate as schizophrenic.

In this connection I am interested in the *physical build* of the patient. As you will notice, she is rather short and thick-set, with round face, and short neck; and she has had a tendency to obesity. You may recall that Kretschmer has written a book in which he attempts to correlate physical build with psychic disposition. His ideas were somewhat novel; but they have received a great deal of attention from both internists and psychiatrists and you will find much comment upon his views in contemporary medical writings.

Briefly put, Kretschmer is of the opinion that what he calls "the pyknic habitus" (or what used to be called "the apoplectic habitus") is prone to be correlated with a certain kind of temperament that he designates the "syntone temperament," that is to say, a temperament that leads the patient to vibrate in sympathy with his surroundings, to enjoy other people, and to mix freely with them. A healthy person of syntone temperament may have oscillations in mood, being sometimes a little elated, sometimes a little depressed, since very few people are exactly even in mood from day to day. But these persons of syntone temperament are, according to Kretschmer, more prone than other people to exhibit those marked disturbances of mood that are known as elation on the one hand, and depression on the other; and if such

persons develop a psychosis it is likely to be of the manic-depressive or cyclothymic type.

The temperament opposite to that of syntone is the "schizoid temperament" (Bleuler). Persons of schizoid temperament are apt to be shy and seclusive, to go their own way, to avoid other people rather than to seek them, and sometimes to take offense easily and, as we say, "to carry a chip on the shoulder." In aggravated cases, still within the boundary of health, such patients, though recluses, may be capable of great performances in scholarship, art, or government. But if these persons of schizoid temperament develop a psychosis they are, according to Kretschmer, very prone to show a schizophrenic trend; indeed, it is they who recruit the ranks of different varieties of dementia praecox, paranoia, and hysteria. According to Kretschmer, persons who exhibit this schizoid temperament are rarely of pyknic habitus. Most often they are of asthenic habitus or of dysplastic habitus. You know what I mean by the asthenic habitus—a tall, thin person with long face, long neck, long flat chest, and visceroptotic abdomen. Such a person is prone to undernutrition rather than to obesity and is apt to have low blood pressure rather than high blood pressure.

Among the persons of dysplastic habitus are included those of outspoken endocrinopathic build (inclusive of hyper- or hypo-pituitary cases, eunuchoid cases, and the like).

Many investigators have attempted to test by careful statistical study the validity of these conceptions of Kretschmer. In this country, particularly, I might refer to the studies of George Draper, of New York, and those of Wertheimer and Hesketh, of Baltimore. Though most students of constitutional make-up tend to admit that there is at least something in these ideas of Kretschmer, they still maintain that one should be careful not to overemphasize their importance and, particularly, not to allow himself to be too much influenced in deciding as to the nature of psychopathic manifestations, merely from a consideration of the physical habitus. Though we may get helpful clues as to psychic predisposition from our studies of physical constitution, we find that there are often very marked exceptions to the general rules laid down by Kretschmer. A person of outspoken pyknic habitus may sometimes develop a schizophrenic state, and, on the other hand, as every psychiatrist will tell you, we do meet with instances of manic-depressive psychosis in certain persons of asthenic habitus.

I think you may be interested in testing Kretschmer's hypothesis for yourselves. Look about among your friends and acquaintances and pick out those of distinctly pyknic habitus, on the one hand, and those of striking asthenic or dysplastic habitus, on the other. Then recall what you can of their emotional tendencies and see whether or not they are predominantly of syntone or predominately of schizoid temperament. I think that you may be very much entertained by this harmless procedure.

Bleuler, the distinguished psychologist in Zurich, maintains that in every personality there are some syntone components and some schizoid components, but that, in most persons, there is a predominance of one or the other set of components. He argues, therefore, that, in any psychosis, there is likely to be predominance either of syntone features (as in the true, affective disorders, or manic-depressive psychoses) or of schizoid features (as in schizophrenic conditions), but, notwithstanding such predominance, the less dominant group of components can color the psychiatric picture. He, therefore, suggests that psychiatrists, instead of asking the question: "Has this man manic-depressive psychosis?" or "Is this man a schizophrenic?" should ask rather the question: "In how far is this man a manic-depressive and in how far is he schizophrenic?"

Many physicians not schooled in the modern psychiatric views might be inclined to look upon the patient before us as merely psychoneurotic. Thus they might speak of her as a "neurasthenic," but the tendency at present is greatly to limit the conception of neurasthenia. Beard introduced the term "neurasthenia" as a designation for a patient who displayed irritability, weakness, insomnia, restlessness, nervousness, mild depression, and the like. Neurasthenia, he thought, was common in persons who were physically rundown and often this disappeared when the patient was subjected to a thorough general upbuilding process.

Of course, the syndrome so designated may be met with in a large variety of conditions; thus, for example, in the early stages of dementia paralytica, such a syndrome is not uncommon, but no one, today, with our newer methods of diagnosis of syphilis and of the parasyphilitic processes, fails to discover the general paresis that is at the bottom of it. Similarly, in epidemic encephalitis after the acute stage has passed, the patient may go through a period in which a syndrome corresponding to Beard's neurasthenia may be met with; but this period is now spoken of as "the pseudoneurastheniform stage of encephalitis." It would obviously be a grave mistake to overlook the organic basis for the syndrome in such cases as these.

Further, in the early stages of schizophrenic states, neurasthenia-like syndromes are sometimes met with, and the physician may temporarily be misled into the diagnosis of a mild psychoneurotic disorder, when in reality he is face to face with the onset of a grave psychosis, which, in many cases, progresses to serious mental deterioration. In my own clinical experience the condition which is most often wrongly designated "neurasthenia" is a depressive phase of a manic-depressive psychosis (in mild form). Many patients who manifest fatiguability, loss of what they call "pep," lack of interest in things they were formerly interested in, headache, insomnia, and mild depression are called "neurasthenics" by family physicians; but if one follow the course of the maladies of these patients, he finds that the symptoms continue for a year or two, after which the patients return to what they regard as normal health,

though when they are what they call "well," they often show a mild elation, being somewhat overhappy, and they are prone to show "pressure of activity," doing then without fatigue far more than the ordinary person can. If one inquire into the life history of such patients he will often find that they have had two or more of such so-called "nervous breakdowns" or "periods of neurasthenia," with intervening periods of "well-being." Moreover, a knowledge of the patient's family will often reveal, on the paternal side, on the maternal side, or on both, similar histories of milder or severer forms of nervous breakdown of the same type, for the manic-depressive constitution is exquisitely hereditary. Many persons, of course, have only one such attack of depression or elation in their whole lifetime, but others have two, three, or more attacks.

The depression in the patient before you is more severe than that ordinarily met with in cases diagnosed as neurasthenia by family physicians. It has, in my opinion, all the earmarks of the depressive phase of a manic-depressive psychosis. Still, it is not of so severe a type as to require treatment in a closed institution, though if suicidal impulses should develop in the patient she should be carefully protected from these impulses and might then be temporarily better off in a closed institution.

A large proportion of the cases treated for "nervous breakdown" outside of asylums and outside of psychiatric clinics, say in the private wards of general hospitals, in sanatoria, or in nursing homes, are in reality cases of depression that belong to this manic-depressive group. In my opinion, many of the patients who are treated by psycho-analysis for one year or for one and a half years before they recover are cases of this type. The patients that fail to recover are more often of the schizophrenic group.

No matter what treatment is pursued during the course of a depressive phase of an elative-depressive psychosis there may be but little change in the patient's state until the depression has nearly run its course. Thus whoever treats the patient in the early stages of the depressive malady may get but little credit, on the contrary much censure, for his therapeutical activities, whereas, whoever is lucky enough to be in charge of the patient in the time of transition from the depressive state to the normal state, or to a slightly elated state, may get a good deal more credit than he deserves. Being in consultation practice myself, I have not infrequently seen patients of this sort after they have had one year or two years of depression and under my observation and treatment they have quickly recovered from the depression. In such instances, however, I have always been perfectly frank with the patients and have explained to them that the same treatment applied earlier in the course of the depression might have done little or nothing in the way of shortening its course. Such depressions must, in my opinion, run their course; Nature brings about the cure and all that we, as physicians, can do is to make the bearing of the symptoms as easy as possible for the patient until the change takes place. Nor is it ever safe to make a definite

prophecy regarding the probable duration of a given depression of this type. Some depressions last only a few weeks or a few months; the average duration is, perhaps, one and a half to two years, but I have known cases in which the depression continued uninterruptedly for as long as five years and, in rare instances, for even ten years or longer, with ultimate recovery. In one and the same patient the periods of depression, when they recur, tend to be approximately of the same duration, but there are exceptions also to this rule; for I have known the nervous breakdowns in the single patient to be of very unequal length. Hence, it behooves us to be exceedingly cautious in making a prophecy; when I have made the clinical diagnosis of this type of depression I tell my patient frankly that, in my opinion, the depression will, in time, run its course and later on the patient will be again as well as before, but, on account of the variability of duration, it is impossible safely to predict the length of time that will elapse before normal feeling and mood will return.

It seems to me a little unfortunate that the name "manic-depressive psychosis" has come commonly to be thought of by both physicians and patients as always meaning a very serious psychotic malady requiring treatment in a closed institution. To label, therefore, the milder cases with this name may be harmful because of the connotation. The term "elative-depressive state" is not quite so objectionable. Since it is the *affectivity* of the patient that is mainly disturbed, in all these cases, whether they are severe or mild, and since the manic-depressive psychoses are, therefore, predominantly affective psychoses, it has been my custom, of late, to designate these states as *affective disorders*, using the adjectives "mild," "moderate," or "severe," according to the degree in which the symptoms appear. This term "affective disorder" is far less objectionable, it seems to me, especially for the very mild forms of manic-depressive psychosis, inasmuch as it does not excite the apprehension of the patient or of the patient's family, as the designation "manic-depressive psychosis" would be likely to do.

These patients with primary depression suffer from a kind of internal *torture*, which is often worse than physical pain. Many patients have said to me that they would much rather have physical pain than the "mental torture" that they experience. I remember one young woman who kept repeating over and over again her wish that she might have physical pain instead of that torture. One morning, as I made my visit to her, the nurse asked me to look at her left shoulder; I did so and saw several elongated blisters. On asking the origin of these, the patient confessed that she had heated her curling-iron red hot and had stroked her shoulder with it, feeling sure that the physical pain would divert her mind from the troublesome mental torture! Of course, what she did was of no avail whatever. She had only added to the total sum of her misery.

DIAGNOSTIC CONCLUSIONS

Summing up the diagnosis in this patient, the essential features would seem to be as follows:

1. Affective disorder with fatiguability, loss of interest, slowing of thought and movement, feelings of sadness, feelings of self-blame and of self-depreciation, weeping spells and mental torture, in a patient who has had many major and minor surgical operations.
2. Gastro-enteropathy with achylia gastrica, postoperative abdominal adhesions, and spastic colon with abdominal pains.
3. Mild secondary anema (hemoglobin 68 per cent).
4. Incipient menopause.
5. Right nephroptosis and slight right hydronephrosis, but without impairment of renal function.
6. Moderate impairment of liver function, as shown by the rose bengal test and the glucose-insulin test.
7. Migraine.
8. Retraction of the thorax after empyema, with pleural adhesions on the left side.
9. Vegetative neurosis with parasympathetic predominance (vagotonia).
10. Deflection of the nasal septum with nasal catarrh.

FURTHER TREATMENT OF THE PATIENT

On account of the floating right kidney and the tendency to hydronephrosis on the right, the suggestion has been made that this patient should have still another surgical operation. The patient herself, as has been said, is rather hopeful that this will be done and she is willing to go through any procedure, particularly any surgical procedure, that offers hope of relief from her pain, but more particularly from her general torture. In my opinion this patient has had fully as much surgery, if not more, already than she should have, and I should certainly avoid any further surgical interference that is not of primary surgical urgency.

The principal malady from which this patient now suffers is, obviously, her affective disorder; and the treatment should be directed toward helping Nature to overcome this. As to the management of the affective disorder, I shall speak in a few moments.

It goes without saying that her somatic ailments should receive due attention. Thus the achylia gastrica merits treatment with full doses of dilute hydrochloric acid with meals, and the spasm of the colon can be ameliorated by novatropine and by the dietetic measures that I have outlined fully in a recent clinic in this place. The secondary anemia can be overcome also by diet, by rest, and by hematinics (iron preparations; elarson tablets after meals, or injections of cacodylate of soda). The migraine has been less troublesome, recently, and I hope that, since

she is at the time of the menopause, she may be, from now on, relatively free from migraine attacks.

Bromide intoxication should be kept in mind and should be tested for, since in patients that have taken large doses of bromides over long periods we can often demonstrate a high bromine content in the blood.

The affective disorder itself requires management away from the patient's home and family and in a neutral environment where good nursing can be provided, as well as close medical supervision. This patient need not be sent to a psychopathic institute; she could be perfectly well taken care of in a nursing home, or in a private room in a general hospital, or, if necessary, in a general medical ward, if the bed be surrounded by curtains separating the patient from the rest of the ward. Whenever possible, it is best for a patient of this sort to be treated outside of her own town, for it is much easier for her if she is far enough away from family and friends to make importunate inquiry regarding her condition difficult. I always insist upon complete isolation of these patients, at least for a time, prohibiting all visits and all letters, requiring the patient to be left in the hands of physicians, nurses, and attendants while the treatment is in progress. The patient must understand, of course, that if anything goes wrong at home, or with anyone who is near and dear to her, she will be told at once and one must exact a promise from the family that they will promptly inform the physician if any untoward event should occur, for it would not be fair to isolate a patient without some such arrangement. Unless the patient be told that something has gone wrong at home, she is to understand that she is receiving daily the equivalent of a message that everything is all right at home. The nurse or the physician, too, should promise to report regularly to the patient's family regarding the condition of the patient, in order that they may be kept in close touch with the progress that is being made.

It is necessary to establish from the very beginning what has been designated "medical obedience," that is to say, the patient should be given to understand that all decisions regarding treatment are to be made by the physician and that she is expected to follow the régime, as outlined, without question. There must be no vacillation on the part of the physician or the nurse with regard to treatment. The establishment of such medical obedience is often made easier at the beginning of treatment by the institution of a period of complete rest in bed and by the administration of the so-called Dubois diet in which 2 or $2\frac{1}{2}$ ounces of milk may be given every two hours during the day for the first day, with increasing amounts daily until, at the end of six days, the patient is taking 2 or 3 quarts of milk in the twenty-four hours. Then the physician may order a change to a full diet with a well-balanced ration, regardless of the inclination or fears of the patient. Many of these patients have food phobias, but the best way to overcome them,

in my experience, is by following the method just outlined. When the time for a full diet has arrived, the patient should be told to eat everything that comes in on the tray whether she feels like it or not and whether or not she fears that some of the foods brought to her may cause gas pains or other symptoms, the physician taking the responsibility for the consequences. Of course, in rare instances, one does meet with an idiosyncrasy for certain foods, particularly where an allergy exists, and, in such instances, the diet will be correspondingly modified. When there is a little anemia, as in this case, a daily hypodermic of cacodylate of soda for a week or ten days may be advantageous and this may be repeated two or three weeks later.

If the patient be markedly undernourished, a gain in weight can often be compelled with great rapidity if 8 or 10 units of insulin be given hypodermically immediately before the principal meal of the day.

When the mental torture is severe, or when there is much anxiety or restlessness, a little sedative may be necessary in these mild melancholic cases. As you know, in the severe melancholias, psychiatrists formerly gave an "opium cure," which consisted of 1 grain of powdered opium in capsule, or the corresponding amount of deodorized tincture of opium three times a day the first day, with increase of one dose per day until as much as 10 grains of opium per day was administered. The patient, of course, never knew what the medicament was. As soon as the mental torture was relieved, the psychiatrist remained at the dosage arrived at for a few days and then decreased the daily intake of opium by one dose per day until the mental torture began to reappear. Then he increased the dose slightly and stayed at that level for a few days, later on reducing the dose again and finally stopping the opium treatment altogether. This opium treatment was undoubtedly advantageous in severe cases of melancholia, though it was not without its risks, particularly if the patient ever found out what remedy was being used. At present, even for the severe melancholias treated in psychiatric institutes, opium is less often resorted to than formerly; instead it is common to give *barbital* in divided doses at 2, 4, and 6 P. M., say 2 grains at a dose and, as a rule, this will sufficiently relieve the torture. In a milder melancholia, such as that of the patient before you, small doses of barbital will doubtless suffice; or you may instead of barbital give $\frac{1}{2}$ grain of phenobarbital three times a day for a time.

Massage given by an experienced person three times a week is often advantageous in the treatment of these patients. Also, some form of *occupational therapy* is very useful, particularly if the teachers of occupation therapy have the kind of personality that will be attractive to the patient and will be stimulative to some effort. If we can get these patients to do something that interests them with their hands, it helps to occupy the time and to make the sojourn away from home more easy to bear. One can have them taught to paint a lampshade, to bind a

book, to weave a rug, to model in clay, or the like. The patient's interest can often be aroused in this way as in no other. After a period of four or five weeks in bed with gain in weight and with general somatic improvement, the patient may be allowed to sit up in a chair for short periods for two or three days and then to begin to walk, keeping all physical effort, however, well within the patient's power. By gradually but steadily increasing the physical activity, a walk of one hour in the forenoon and of one hour in the afternoon can often soon be undertaken.

During all this time there should be daily visits from a physician whose psychotherapeutical conversations with the patient can go far toward ameliorating her condition. She can gradually be made to understand the nature of her malady and the course that it is likely to take. The complete diagnostic survey made before the starting of the treatment goes far toward increasing the patient's confidence in her physician and toward relieving her mind of the fear that perhaps some physical malady exists that the physician has not discovered. Any mental conflicts may be gradually disclosed and solved. The patient must be taught to bear her symptoms as philosophically as possible until they pass; and she should be told that being angry at herself because she is not able to "rise above the symptoms" is harmful since it only increases the strain.

Physicians who do not understand these maladies and who tell the patients that there is nothing wrong with them, that they should "buck up" and "be brave," and that if they will only assume the proper mental attitude their troubles will disappear, make, in my opinion, a grave mistake; for the symptoms in these patients are quite outside their will power and their morality. They are already blaming themselves too much for the condition in which they are. They know that they cannot help the symptoms; and when a physician tells them that they can, they realize, at once, that he does not understand them and they lose confidence in him. Such patients need sympathetic understanding by a physician who has had a certain amount of psychiatric experience and who will guide them in a kind but firm way while Nature is restoring them to more normal affectivity.

The physician can help the patient, too, by the selection of suitable books; and he must be guided in this by the mental level and the previous training and interests of the patient. There are several little books of psychotherapeutical value from which a physician may select. One of the best of these is the small volume by A. P. Call, entitled "The Freedom of Life"; it preaches the gospel of "relaxation" and of "nonresistance" to symptoms while the malady persists. One may tell the patient that she may find in it some things that do not apply to her but that she may take from it anything that she finds helpful. But still better reading will be found in suitably chosen biographies; the physician will often do well, as Dr. Gerald Webb has emphasized, to pay much attention to the "prescription of literature."

It goes without saying that the psychotherapeutist must, himself, be a person who has good self-control, and he must know how to establish a favorable affective *rapport* with his patient. This is usually easy with patients of syntone temperament, though it may be impossible with some patients of schizoid temperament.

The patients with affective disorders should stay under medical supervision *until they are well;* and the resumption of relationships with family and friends should be gradual. It may be wise for the patient to spend a time with the nurse away from home for a period, before returning to home life. Many physicians make the mistake of discharging these patients too soon. If one carry out the treatment patiently and wisely, the results are gratifyingly rewarding.

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RECURRENCE OF HYPERTHYROIDISM AFTER RESECTION OF THYROID GLAND FOR BASEDOWIFIED COLLOID STRUMA; QUESTION OF ASSOCIATED THYMUS HYPERPLASIA; DISCUSSION OF FURTHER MANAGEMENT OF THE CASE[1]

THE patient sitting here has had a return of the symptoms of hyperthyroidism after a subtotal thyroidectomy. I should like to discuss the possible reasons for this recurrence as well as the further management of the case. I shall ask Dr. Paul Michaels to give you, first, a brief summary of the clinical history.

SUMMARY OF THE CLINICAL HISTORY

The patient, Harry R., a white married man, laborer, thirty-four years of age, is a patient on the service of Dr. McVey in our hospital.

Born in North Carolina where he remained until he was five years of age, he lived for the following twenty years in the state of Washington and since then has been resident in California.

He was very well until November, 1928 (a little over one year ago), when he began to be nervous, to feel weak, to have excessive thirst and an increased appetite, and to notice that he perspired very freely. Between November and February he lost 25 pounds in weight. He then had his tonsils removed. In March, 1929, the thyroid gland became enlarged and his basal metabolic rate was found to be 73 per cent above normal.

He entered Highland Hospital on June 3, 1929, where his basal rate was found to be 93 per cent above normal. He was given Lugol's solution, 10 minims three times a day after meals, and at the end of five days his basal rate was found to be 26 per cent above normal. On June 14th, a subtotal thyroidectomy was performed. Pieces of the thyroid examined histologically brought a report from the pathologist of "colloid goiter." He was discharged from the hospital on June 22d, feeling very much better.

By autumn, however, the symptoms had recurred and he reentered the hospital on November 17, 1929. Both lobes of the thyroid were still palpable, the left being larger than the right. He exhibited marked tremor, excessive perspiration, and nervousness. *x*-Ray examination showed no evidence of substernal thyroid nor could any definite thymus shadow be made out. There was slight exophthalmus and he had other eye signs; the pulse rate was 100. His basal rate had again become 61 per cent above normal, though eight days later (on 5 minims of Lugol's solution three times a day) it was found to be only 35 per cent above normal. His Wassermann reaction is negative and examinations of the blood and urine have yielded results within normal limits. The patient is some 22 pounds under calculated ideal weight.

DISCUSSION OF THE CLINICAL DATA

The clinical picture presented by this man is undoubtedly that of thyreo-intoxication. The cardinal symptoms of struma, tachycardia, and exophthalmus have been present and he has also had a fine tremor,

[1] Clinic before the Alameda County Medical Society, December 16, 1929.

though it is not very marked at the present time. The excessive sweating and the nervous symptoms are also a part of this hyperthyroid picture. Most important of all has been the very high basal metabolic rate.

Though the histologic report of the thyroid excised was "colloid goiter," we can feel fairly sure that, in this gland, there must be islands of hyperplasia of the gland tissue that account for the overproduction and excessive outflow of thyroid secretion. It is possible, too, that through some constitutional peculiarity this man's tissue cells react in an abnormal way to thyroid secretion.

On account of the excessive thirst and the increased appetite of the patient, the urine was carefully examined for sugar and much sugar was found to be present. An examination of the fasting blood sugar, however, revealed no hyperglycemia. Evidently the renal threshold for sugar excretion by the kidneys in this man is low.

It would have been interesting to have tested a portion of the struma removed, for its iodine content. In colloid goiter the iodine content is sometimes high, whereas in the hyerplastic goiter of typical Graves' disease the iodine content is low. More interesting still would have been an experiment upon growing tadpoles with extracts of the removed thyroid. I am very much interested in the experiments that are being carried on by Dr. Jordi in the Hooper Institute in San Francisco. He finds very great differences in the influence of different thyroids upon the rate of growth, and especially upon the rapidity of metamorphosis, of growing tadpoles. This method of investigating the method of thyroid tissue, introduced by Wegelin and Abelin, has given some truly remarkable results.

Despite the negative *x*-ray findings, one cannot help but feel that there may be a thymus hyperplasia in this man. There are some cases of Graves' disease that have not recovered after thyroidectomy but have later been very favorably influenced by resection of the thymus, as the experience of Haberer has shown. The increase of the oxidation processes in this patient, of course, accounts for his emaciation, though it is interesting that loss of weight does not always go parallel to increased metabolic rate. There is always increased destruction of protein in these patients with hyperthyroidism.

The pathogenesis of exophthalmic goiter is still far from clear. Why the thyroid gland should become hyperactive has not yet been satisfactorily demonstrated. Some think that there is a primary change in the sympathetic nervous system, perhaps in the sympathetic centers in the hypothalamus of the brain.

The very remarkable effects of iodine when administered to thyroid patients also await a full explanation. Surgeons now almost invariably use Lugol's solution in good doses in order to prepare the patient for operation. The basal metabolic rate falls rapidly and the toxic symptoms

are diminished within a few days. As you know, however, the effect is only temporary.

In contrast to these large doses of iodine, very minute doses will also, if given over a long time, often favorably affect the clinical picture.

FURTHER TREATMENT OF THE PATIENT

Surgical therapy is much more popular than medical therapy for cases of thyreo-intoxication. This has been mainly due to the quick results that follow operative removal of a portion of the gland. Patients who cannot afford a long-continued medical treatment for economic reasons welcome, therefore, the quick result that surgery yields.

In patients like this one, however, where a removal of the large part of the thyroid gland has not prevented a return of the symptoms, one has to decide upon the next therapeutical step. This man has had a marked recurrence of his symptoms, as you see, and we have to decide whether he should be subjected to another operation or whether other methods of treatment might be sufficiently helpful.

It is quite possible that with minimal doses of iodine and with a carefully conducted *x*-ray therapy this man might improve satisfactorily. If *x*-ray treatment be given, however, it should be most cautiously applied, for in some cases the patients are made worse by injudicious radiation of the gland; in other cases, when too large doses have been given, a hypothyroidism with myxedema has developed. Formerly, some surgeons objected to *x*-ray treatment of the gland, inasmuch as they feared that adhesions would be formed that would make subsequent operation more difficult. This fear, however, is not justified, as later experience has shown.

Some investigators have lauded the combined administration of small doses of iodine together with thymus gland, giving 0.6 Gm. of thymus per day (Liebesny). It is to be remembered, however, that thymus preparations appear to vary enormously in their activity. It seems to be important to secure the thymus from young animals.

Injections of calcium chloride and gelatin (5 to 7 cc. of Merck's "Kalzine") have been lauded, as well as injections of "Gynergen." It is asserted that the thyreotoxic phenomena diminish under these forms of treatment.

Rest and quiet are very important for these patients. Any emotional excitement, or any overstrain, either physical or mental, exaggerates the symptoms. Galvanization of the sympathetic has been used, but I have never seen much benefit follow it.

During the past few years I have seen many patients with mild Graves' disease respond very favorably to small doses of phenobarbital given after each meal. Some physicians give the drug, for a time, in doses sufficiently large to make the eyelids droop a little!

It is important to make the patient gain weight, but one should

give a diet that is rich in carbohydrates and fats and relatively poor in proteins. Sometimes an injection of 6 or 8 units of insulin before the principal meal will help a patient to gain weight. I should like very much to hear Dr. Kerr comment upon this case, inasmuch as he showed me recently another case of hyperthyroidism at the University of California Hospital in which there had been a recurrence of symptoms after operation.

DR. KERR: We are very interested in these recurrences of thyreo-intoxication. We are trying systematically, in different groups of cases, the effects of different forms of medical treatment upon thyreo-intoxication. Thus we have been using Lugol's solution in some cases and, in other cases, minimal doses of tincture of iodine. We are also trying in another group the effects of *x*-ray treatment. We hope to carry these experiments over a considerable period in order to have enough cases to permit of sound judgment as to the results obtained.

DR. BARKER: Dr. Kerr has made a very careful study of the regional incidence of goiter. As I understand it, goiter is not especially prevalent throughout California, though there are certain valleys and certain regions in the foothills of the mountains in which goiter is quite prevalent. You will be interested to learn that the vegetable growers of certain southeastern states are whispering that there is not enough iodine in the fresh vegetables grown in California and that, therefore, inhabitants of the East should patronize eastern products! This man tells me that perhaps he ought to have stayed in the Carolinas where he was born, but I suppose that someone of you will jocularly argue that perhaps the original injury to his thyroid was due to his birth and early residence in the Carolinas!

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CONTROL OF DIABETES IN HEMOCHROMATOSIS; REMARKABLE IMPROVEMENT IN THE STRENGTH AND WORKING CAPACITY OF A PATIENT WITH DECREASE OF HIS PIGMENTATION UNDER DIET AND INSULIN THERAPY[1]

THE patient whose malady is to be discussed in the clinic this morning is well known to the staff and to some of the earlier students of this medical school for he has been under observation for over three years and was one of those patients who formed the basis for the case study of hemochromatosis published by Drs. T. L. Althausen and Wm. J. Kerr some two years ago. Though he had begun to improve markedly at the time their report was published, sufficient time has since elapsed to prove not only the possibility of a long period of control of bronzed diabetes with the newer methods of therapy, but also the possibility of improvement of the hemochromatosis itself, at least insofar as the cutaneous pigmentation is concerned. I am glad to have the opportunity of discussing the case with you, not only because of its intrinsic interest as an outspoken example of hemochromatosis with pigmentation of the skin, with diabetes, and with damaged liver, but also because it is important to place on record the experience in maintaining the well-being of a patient over so long a period, an experience which, as far as I know, is unique.

The damage to the liver that occurs in hemochromatosis modifies in very remarkable ways the course of the accompanying diabetes. To these modifications of the diabetic picture and to the special modifications of the insulin therapy that must be made in such cases, I shall take occasion during the hour to refer.

CASE HISTORY

The patient, Daniel O., age fifty-six years, was first admitted to the University of California Hospital on November 24, 1926, where he remained under observation and treatment until January 28, 1927.

His main *complaints* on admission were of general weakness, increased thirst, the passing of large quantities of urine, a ravenous appetite, and cramps in the legs.

Family History.—Aside from the fact that several members of the patient's family have but little hair upon the body (hypotrichosis), the family history is without evident bearing upon the patient's malady.

The patient married at thirty-nine and is the father of three children, who are living and well.

[1] Amphitheater Clinic, University of California Medical School, December 11, 1929.

Previous History.—Born in Ireland, the patient was a farm laborer in that country until his twenty-seventh year when he came to America. He was engaged here in digging trenches for the laying of gas pipes for about twenty years; since then he has been occupied as a night watchman.

He seems to have been very healthy in early life, reporting only one illness—an attack of influenza at forty-four. As to traumatic experience, he fractured his right ankle at fifty-one, requiring hospital treatment for several days and rest at home for two months. He has never been operated upon and he denies having had venereal disease.

The patient has not been one to complain of minor symptoms, but on close questioning it was found that he had been deaf since the age of forty-one and that he has had ringing in the ears at times. He has had much treatment from dentists because of caries and pyorrhea. Aside from an occasional diarrhea there had been no symptoms referable to the gastro-intestinal tract. During the preceding three or four years he had noticed occasional, slight swelling of the ankles. He had had occasional headaches and for eight or nine years had often suffered from cramps in the legs during the night. Recently these cramps had become more pronounced. He had been sensitive to cold for three years before entry to the hospital in 1926.

He himself had noticed the sparseness of the hair on his body; his beard had been so scanty that he shaved only twice a week.

As to his habits, there had been excessive indulgence in strong alcoholic beverages, though since Prohibition he drank less than formerly. There were times, however, when he drank a glass of whisky every morning before breakfast.

History of Present Illness Given in 1926.—Though there are symptoms mentioned in the previous history that doubtless belong in reality to the present illness, still the patient himself asserts that he felt perfectly well until two months ago when he first noticed extreme thirst. He drank large quantities of water and this compelled frequent and abundant urination during both night and day. He admitted that he had noticed darkening of the skin of his legs for one week before admission.

Asked regarding his appetite, he asserted that he had noticed no increase; but, when asked as to the variety and quantity of foods that he ate, it was evident that he must have had a ravenous appetite and that he had eaten excessively. Some six weeks before applying for treatment he had noticed that he was becoming very weak and that the cramps in his calves that had been occasionally present during the preceding eight or nine years were becoming more frequent and more violent.

Ten days before admission he had begun to grow dull and drowsy. His physician told him that he had diabetes and outlined a diet for him but advised him strongly to enter the hospital for thorough study and for the planning of a proper dietetic regimen. The patient felt that he could not afford to go to a hospital and grew steadily worse until, finally, he decided to visit the Out-patient Department here. His urine was then found to be loaded with sugar and acetone bodies; and his fasting blood sugar on the following day was 336 mg. per cent. The patient was, therefore, sent into the Stationary Clinic for immediate treatment, inasmuch as the dangers of diabetic coma were evident.

Studies in the Hospital.—On entrance to the hospital ward he was given immediately 200 cc. of orange juice and 25 units of insulin every two hours and heat was applied to the legs. Shortly after his fourth dose of orange juice and insulin he became quite stuporous and rambled in his speech; his face became flushed, and he began to perspire excessively and to complain of increased hunger. He was given 200 cc. of orange juice immediately (of course without more insulin) and the symptoms cleared up promptly. This early evidence of "insulin shock" was so startling that the patient's insulin dosage was reduced to 15 units along with 200 cc. of orange juice during the period that immediately followed. However, at 9.30 the next morning he again gave evidence of insulin shock, his face becoming very flushed and his psyche was obtunded within fifteen minutes after receiving the insulin. As by this time his urine had be-

Fig. 19.—Extensive brown pigmentation of legs in the case of D. O'L., with hemochromatosis. Plate was made from colored print. (Althausen and Kerr in Endocrinology, vol. xi, 1927.)

come sugar free as well as acetone free, he was placed, temporarily, upon a diet of 30 Gm. of protein, 20 Gm. of fat, and 30 Gm. of carbohydrate, to which was added orange juice at meals and between meals. The insulin was, for the time being, discontinued.

Physical Examination.—He was found to be emaciated and to look older than his age. The skin was dry and scaly, except during the periods of insulin shock. The legs were deeply pigmented and of a brown color (Fig. 19), as were the backs of his hands. There was also a peculiar grayish, slaty discoloration of the arms, face, and neck, but no abnormal pigmentation of the mucous membrane could be detected. There was general hypotrichosis. He was partially bald, the eyebrows were sparse, there was but little beard, and there was an entire absence of hair in the axillae and over the chest. The pubic hair was also scanty with transverse upper delimitation (feminine type).

There was slight enlargement of the lymph glands in the right axilla and in both groins. The dilated venules of the nose and the watery eyes of the patient suggested the "hepatic facies" of an alcoholic patient. The pupils reacted normally, but they were small and somewhat irregular in outline. Ophthalmoscopical examination was negative except for retinal arteriosclerosis. The mouth was poorly cared for; there was evidence of pyorrhea. The eardrums were retracted and the patient was found to have partial bilateral deafness.

The chest was of emphysematous type, but the lungs, aside from emphysema, were negative. The apex of the heart was displaced somewhat to the left. Peripheral arteries were thickened and tortuous. The blood pressure was 96 systolic, 70 diastolic. There was no evidence of valvular heart disease.

The abdomen was protuberant, but the umbilicus was not everted and there were no signs of fluid in the abdominal cavity. The liver, however, was of enormous size, filling the whole upper abdomen down to the level of the umbilicus. The edge of the liver was easily palpable and firm, but not tender nor nodular. The spleen was not palpable. The external genitals were slightly hypoplastic and the testes were smaller than normal. The prostate was also small. There was slight clubbing of the fingers with acrocyanosis. A few varicose veins were seen in both legs.

Laboratory Examinations.—*Blood.*—Red blood cells, 4,030,000; white blood cells, 7400; hemoglobin, 92 per cent (Sahli). Differential count normal. No anisocytosis or poikilocytosis. Platelets were present in normal numbers. Fragility test normal. Bleeding time, three and a half minutes. Coagulation time, seven and a half minutes. Wassermann reaction in the blood serum, negative.

Fasting blood sugar 336 mg. per cent. Icterus index 11. Carbon dioxide tension 64.7 cc. (bound as bicarbonate) per 100 cc. of serum. Nonprotein nitrogen 33.6 mg. per cent. Urea nitrogen 15.4 mg. per cent. Uric acid 3.4 mg. per cent. Creatinine, 1 mg. per cent. Blood cholesterol 156.7 mg. per cent. Plasma chlorides 5.97 Gm. per liter. Serum protein 6.5 per cent.

Urine.—On admission the urine contained large quantities of sugar, and acetone and urobilin were present. Under treatment, the urine soon became free from both sugar and acetone and was afterward kept free. Hemosiderin granules were found in tail-shaped cells by Pearl's method and this same blood pigment was also demonstrated in epithelial cells of the sediment by the method of Mallory and Wright. Tests for melanin in the urine were negative.

Stool.—Negative except for evidences of putrefaction.

The *basal metabolic rate* on admission was 19.6 per cent plus and on the following day was 34.4 per cent plus, after which there was a gradual fall to 4.1 per cent plus.

Stomach contents were negative.

Rose Bengal Liver Function Test.—Several of these tests were made but the results indicated that there was no impairment of the dye excretion on the part of the liver, despite the fact that it was large and firm. *Renal function* tests showed but little impairment.

x-Ray reports were negative except for enlargement of the heart, dilatation of the aorta, and spasm of the duodenal cap.

Electrocardiogram.—P-R interval of 0.19 second, approaching partial A-V block; flattened T_1, diphasic T_2, indicating myocardiopathy.

Biopsy of the enlarged lymph glands and of sections of the skin were reported upon by Drs. Millzner and Bartlett. In the enlarged lymph glands hemosiderin pigment had been deposited, especially in endothelial cells and in the reticulum (Fig. 20). There was also some hemofuscin present. In the sections of the skin hemosiderin was profusely present in the corium. Small masses and clumps of pigment could be seen just beneath the epidermis and about the blood vessels and sweat glands (Fig. 21). Hemofuscin was demonstrated in coarse masses beneath the epidermis (Fig. 22).

Fig. 20.—Daniel O. Hemochromatosis. Section of lymph node showing brownish-red, highly refractile, granular masses of hemofuscin.

Treatment in the Hospital.—After the glycosuria and ketonuria had been overcome, the severe cramps in the legs quickly disappeared. With maintenance of the antidiabetic regimen the patient was also placed, at the end of one week, upon 50 mg. of ephedrine three times a day; this was followed by an increase of from 10 to 12 mm. in the systolic blood pressure during the next three weeks. The cutaneous pigmentation deepened during the first month in the hospital and the size of the liver remained unchanged during his two months' stay. The patient's strength, however, rapidly improved.

Supervision in the Out-patient Department.—During the subsequent period, the patient was allowed to live at home but was to report at weekly intervals at the Dispensary. He adhered to his diet and to his insulin dosage fairly faithfully. He gained in strength and weight and was permitted to work again as a night watchman.

Gradually, the pigmentation of the skin over the legs, arms, neck, and face grew lighter.

The case was reported by Drs. Althausen and Kerr in 1927 with the following clinical diagnoses:

Hemochromatosis; pigmentation of the skin; diabetes mellitus with acidosis; cirrhosis of the liver; inguinal and axillary lymphadenopathy; sexual hypoplasia; arteriosclerosis; hypertension; chronic myocarditis with cardiac hypertrophy; pulmonary emphysema; pulmonary osteo-arthropathy; catarrhal deafness.

Interval History.—Since leaving the hospital in January, 1927, the patient has been followed in the Out-patient Department. He weighed only 104 pounds when he left the hospital. On a diet of 1765 calories, consisting of 70 Gm. of protein, 125

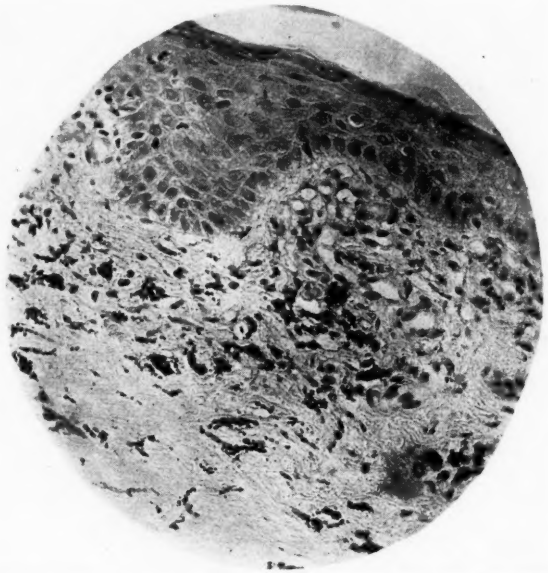

Fig. 21.—Section of skin in case of hemochromatosis (patient Daniel O.), showing the diffuse distribution of small lumps of hemosiderin granules which are stained black by ammonium sulphide.

Gm. of fat and 90 Gm. of carbohydrate, and with 49 units of insulin daily he gained 21 pounds during the first two months, his weight reaching 125 pounds. His highest weight since then has been 137 pounds. He now weighs 128 pounds, so that he is still considerably underweight.

In September, 1927 he developed an ulcer on the cornea of his right eye, which responded readily to treatment. In October, 1927 a scaly, eczematous type of eruption appeared on the arms; it was bilaterally symmetrical. Three months later it had spread to the lower extremities, the abdomen, and the area between the scapulae. Desquamation occurred and the skin beneath showed a very marked decrease in pigmentation. The pigmentation has increased since then, but it has never reached the degree of severity which was present when he was admitted to the hospital in 1926.

The diabetes has shown considerable improvement. At present the patient is on a diet of 2220 calories, which gives him 80 Gm. of protein, 140 Gm. of fat, and 160 Gm. of carbohydrate. He is now receiving 40 units of insulin each day. His fasting blood sugar, taken two days ago, was 98 mg. per 100 cc. of blood. He is able to carry on his work as a night watchman and he says that he "feels well and strong."

DISCUSSION OF THE CASE

The progress of this patient since 1926 has, considering the grave nature of his disorder, been extraordinarily satisfactory. In the old days, this patient with so severe a diabetes could not have survived at

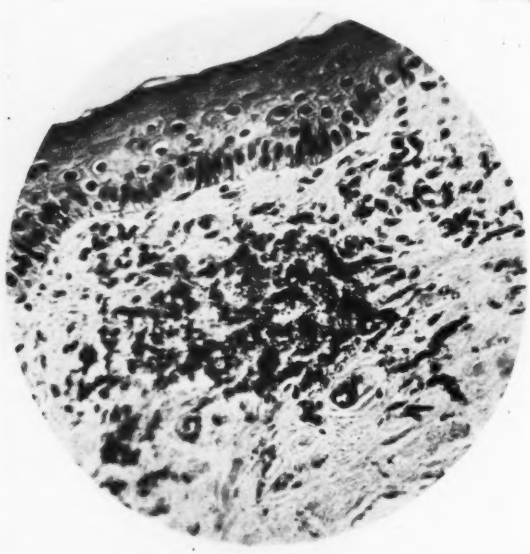

Fig. 22.—Section of skin in case of hemochromatosis (patient Daniel O.), demonstrating the occurrence of hemofuscin in large masses just beneath the epidermis. Hemofuscin stains brownish red with carmine.

all; but even since insulin has become available the management of the diabetes in a case of this sort is not without its difficulties. The extraordinary tendency to insulin shock, on the one hand, and the marked tendency to reappearance of acidosis, on the other, are features worthy of special comment.

The Peculiar Tendency to Insulin Shock.—The frequent occurrence of insulin shock in this patient has already been referred to. Dr. Althausen tells me that during his two months' sojourn in this hospital (November 24, 1926 to January 28, 1927) he had no less than seventeen

hypoglycemic reactions and it was found that the patient was safe from such insulin reactions only when his blood sugar was in the neighborhood of 200 mg. per cent. In ordinary simple diabetes we can usually reduce the blood sugar to 100 mg. per cent and keep it there, but any attempt to bring about a result of that sort in this patient was sure to be followed by a severe insulin reaction. In some instances the blood sugar fell to 16 mg. per cent!

The clinical symptoms accompanying the hypoglycemic shock were usually pronounced (flushing of the face, excessive perspiration, and complaints of hunger, followed by restlessness, mild delirium, rambling speech, and coma). Moreover, instead of responding promptly to glucose and orange juice given by mouth, the patient would often require very large amounts of glucose and orange juice by mouth for several hours before recovering. So different were these severe reactions from those met with in ordinary diabetes that the staff began to wonder whether or not they were really due to hypoglycemia, but the blood sugar determinations definitely corroborated the view that a true hypoglycemia was the cause. Here an interesting observation was made. Orange juice and glucose by mouth were only very slowly effective, as I have said, but 20 cc. of a 50 per cent glucose solution given intravenously aroused the comatose patient within one half minute after the injection was started and at the end of one minute he was entirely over his hypoglycemic symptoms!

Another interesting observation was made in this patient in that it was found that very slight increases of carbohydrate intake were sometimes followed by increases in the blood sugar content out of all proportion to the changes in diet. Dr. Kerr and Dr. Althausen concluded, and I believe with right, that there is in this patient, in addition to his diabetes, a very marked disturbance of the function of regulation of the blood-sugar level—something foreign to our experience in ordinary pancreatic diabetes. The suggestion made in this clinic that the damage to the liver accounts for this disturbance of the regulation of the blood-sugar level is most interesting and is worthy of further investigation. It will be important to try to determine in how far this depends upon disturbed glycogenesis, on the one hand, and in how far upon disturbed epinephrine mobilization of hepatic sugar, on the other.

The observations in this case of the very slow effectiveness of glucose and orange juice by mouth, when intravenous glucose was promptly effective in overcoming the hypoglycemic shock in this patient, would seem to point to some disturbance of the absorptive power of the mucosa of the alimentary tract at the time when the shock was experienced.

The Marked Tendency to Acidosis.—Your experience in this patient with regard to the strong tendency to the formation of acid bodies corroborates the experience of the Argentine observers, Hernandez and Benaros, with a similar patient. Your patient was found incapable of

metabolizing fats under conditions in which a patient with simple diabetes might be expected to metabolize them satisfactorily. Here again you resort to the liver damage as an explanation of the disturbed fat metabolism. The suggestion is quite compatible with the contemporary view that one of the main functions of the liver is to produce from fats and proteins certain intermediate carbohydrate substances and that the ketone bodies of diabetic acidosis are to be looked upon as inadequately metabolized fragments of fat molecules that are being transformed into such intermediate carbohydrate substances.

Prognosis.—Undoubtedly, the prognosis of diabetes in hemochromatosis is rendered somewhat graver than that of simple pancreatic injury because of the accompanying liver damage that disturbs the blood-sugar-level-regulating function and the fat-metabolizing function. Nevertheless, your experience with this patient has proved that, with thoughtful management of the diet and of the insulin administration, it is possible, not only to rescue the patient from diabetic coma and to prolong his life, but also to restore for a long time his working capacity and, to my astonishment, to decrease his cutaneous pigmentation.

One's apprehension lest the continual presence of a blood-sugar level of 200 mg. per cent might be harmful to the peripheral nerves of the patient and to the functional level of the still active islands of Langerhans of the pancreas is somewhat allayed by the facts that the painful cramps in the patient's legs have disappeared and that the studies of the physiologist Macleod with depancreatized dogs have indicated that quite high blood sugars can be permitted for years without any apparent impairment of the general health of the animals.

The danger of the development of carcinoma of the liver in patients exhibiting hemochromatosis must from now on be kept in mind, since cases illustrative of this complication have recently been reported.

THE ORIGIN OF HEMOCHROMATOSIS

There has been much dispute as to the etiology and pathogenesis of the fundamental process of pigment deposition in hemochromatosis. Many theories were advanced, but nearly all of them have been shattered. We now believe that the diabetes and the cirrhosis of the liver are processes secondary to the pigment deposition and not primary disorders. We also know that the disease is not due to increased hemolysis, for the osmotic resistance of the red blood corpuscles of the patient is not diminished. You will recall that the fragility test in this patient was found to be normal. We have, therefore, to fall back upon some obscure perversion of iron metabolism as an explanation; for some reason or another, in the degradation of hemoglobin, the normal process is deviated from and the pigments (hemosiderin and hemofuscin) are deposited at sites that, for some reason as yet unknown to us, seem to have an especial affinity for them. Secondary to the deposition of the

pigment and the chronic irritation that it produces, a chronic fibrous inflammation develops with sclerosis of the organs involved (fibrous pancreatitis; cirrhosis hepatis; chronic splenitis; chronic lymphadenitis, etc.).

FURTHER MANAGEMENT OF THE PATIENT

As a result of the experience with this patient, no attempt will be made to keep his blood sugar at a lower level than 200 mg. per cent. He will be continued to be kept, therefore, on a diet that contains 1765 calories, which gives him 27 calories per kilogram of body weight. In this diet the ratio of fatty acids to glucose is 1. At times the patient's caloric intake can be raised to 1800 or a little higher.

The amount of insulin necessary to keep the blood-sugar level around 200 mg. per cent has varied from 50 to 55 units per day, given in three divided doses. We must hope that he will continue to do well.

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MELANOTIC PIGMENTATION OF THE SKIN AND MUCOUS MEMBRANES ASSOCIATED WITH LOW BLOOD PRESSURE AND SEVERE GASTRO-INTESTINAL DISTURBANCES (ADDISON'S DISEASE OF THE SUPRARENAL GLANDS)[1]

WHEN there is characteristic pigmentation of the skin with deposits of melanin in the skin and in patches in the oral mucosa, when the blood pressure continues to be very low, when there is marked asthenia, and when there are disturbing gastro-intestinal symptoms, one can make the diagnosis of Addison's disease of the suprarenal glands with a great deal of assurance. But there are many cases in which the diagnosis is by no means easy, particularly if one of these cardinal symptoms be absent or be but slightly marked. In the early course of the study of the present case a good deal of doubt was expressed as to the exact nature of the illness; some thought that they had to deal with a case of Addison's disease; others felt that the criteria were insufficient for the making of a positive diagnosis. It will be interesting to examine the patient today, after hearing his history, and to see whether or not we are justified in arriving at a positive conclusion.

CASE HISTORY

The patient, George O., a white man thirty-eight years of age, has been twice in the hospital: (1) From October 5 to November 21, 1929, and (2) just now, when he entered in order to be checked up and to appear at this clinic.

His *complaints* (in early October) were of nausea and vomiting, of two weeks' duration, and dizziness.

Past History.—The patient suffered from the ordinary diseases of childhood and, in addition, had smallpox when seven years old and gonorrhea at thirty-six. He was operated upon for hernia at twenty-three and had a laparotomy for removal of the appendix at thirty-three.

He is a Hungarian by birth and by occupation he is a blacksmith.

Family History.—Negative for tuberculosis and for diseases resembling his own.

Present Illness.—Toward the end of September, 1929, the patient was suddenly taken ill with nausea and vomiting. The vomiting appears to have been definitely projectile in character, and the vomitus consisted of large quantities of yellowish fluid.

During the following two weeks the patient vomited on the average once a day, usually about an hour after the evening meal. He felt very ill and became ever weaker. He complained also of frequent attacks of dizziness.

On inquiry it was found that nearly two months earlier the patient had noticed that his skin was growing darker in color and that it looked as though it were tanned, particularly on his forearms; he noticed also small white areas outlined against the tan. In the past the patient has always had a white skin and he comes from a family in which the skin color is light. He has not been especially exposed to the sun.

[1] Amphitheater Clinic at the University of California Medical College, December 11, 1929.

He gave no history of headaches, of palpitation, or of previous gastro-intestinal disturbances, nor could any symptoms suspicious of tuberculosis be elicited. He has had no cough, no pain in the chest, no hemoptysis, and no night sweats, nor has he been exposed to tuberculosis, as far as he knows. The only other symptom earlier complained of has been that of rising to pass urine three or four times at night during the past two years.

Physical Examination (*First Admission*).—The skin of the forearms and hands is rather deeply pigmented; that of the upper arms is of a yellowish tint. The pigment, however, is not markedly increased in the armpits. The skin of the face is of a yellowish tint, as is that of the thorax. The skin over the abdomen shows increased pigmentation, as does also that over the lower extremities.

Some small areas of brownish pigmentation can be seen within the mouth, especially about the lower teeth. The lips are somewhat cyanotic, the tonsils are enlarged and reddened and there is injection of the pharynx. The cervical lymph glands are slightly enlarged. The heart and lungs are negative; the blood pressure is 90 systolic, 44 diastolic; the genitals are negative.

Neurological Examination.—The deep reflexes are obtained but are sluggish.

Laboratory Examinations.—*Blood.*—Red blood cells, 4,300,000; hemoglobin, 84 per cent (Sahli); white blood cells, 5100; differential count: neutrophils, 45 per cent; eosinophils, 1 per cent; mononuclears, 49 per cent; monocytes, 6 per cent; eosinophils, 1 per cent. Platelets normal.

Urine.—Normal in all respects.

Vomitus consists of liquid with undigested food products. It contains no occult blood and no free hydrochloric acid.

Wassermann Reaction.—Negative.

Basal Metabolic Rate.—Four and five tenths per cent below normal for age and sex.

Stool.—Negative.

Blood Chemistry.—Blood sugar fasting 0.09; sugar tolerance test normal; blood creatine 5.19 mg. per cent before starting suprarenal extract.

In another test before starting suprarenal extract, blood creatine 1.35 mg. per 100 cc.; blood creatine and creatinine 3.84 mg. per 100 cc.; total volume of urine 2545 cc., the creatine and creatinine 1.06 Gm.; creatine 1.02 Gm.; creatine and creatinine 0.04 Gm.

After giving suprarenal extract for two weeks, blood creatinine and creatine 4.28 mg. per 100 cc. *Urine.*—Total volume 3330 cc.; creatine and creatinine 1.35 Gm.; creatinine 1.222 Gm.; creatine and creatinine 0.13 mg.

x-Ray Examinations.—Heart rather small; lung fields clear; some thickening of the pleura over both apices. Gastro-intestinal tract negative except for spasticity of the cap, which was probably due to reflex irritation. No evidence of calcification in the region of the suprarenal.

Biopsy of Skin.—Shows marked melanosis.

Electrocardiogram.—Rate 72, rhythm normal. P_1 notched, EK within normal limits.

Diagnosis (*First Admission*).—Acute gastro-intestinal upset of unknown etiology; the possibility of Addison's disease to be kept in mind.

The patient was treated for the vomiting by gastric lavage and by hypodermoclysis. He was kept at rest in bed and was given McLean's extract of suprarenal gland three times a day.

Course in the Hospital.—He vomited during the first five days, but this was soon relieved by the lavage. He grew stronger when his vomiting ceased and led quite an active existence, becoming able to climb hills. At no time was he at all markedly asthenic. The blood pressure, however, continued to be very low, sometimes as low as 80 systolic, 46 diastolic. The maximal pressure observed was 106 systolic and 50 diastolic (after taking McLean's suprarenal extract).

The patient left the hospital feeling much better. He was afebrile and his

muscular strength had increased. He was advised to limit his activity for two weeks, to take a high caloric diet and to take McLean's suprarenal extract three times a day.

DISCUSSION BY STAFF MEMBERS

It was the opinion of Dr. Falconer that the possibility of Addison's disease should be seriously considered because of (1) the peculiar deposits of pigment in the buccal mucous membrane with generalized pigmentation over the entire body, (2) the vomiting, (3) the low blood pressure, and (4) the suggestive findings in the chest. He felt that the strong point against this diagnosis was the lack of marked asthenia.

It was thought by Dr. Lisser that except for the suggestive finding of pigmented areas in the mouth, the evidence was insufficient for diagnosis of Addison's disease at the time.

In a note made by Dr. Miller it was stated that the entire buccal mucosa was of a brownish, yellowish tinge. On the mucous membrane of the lips are many irregular pinheads, and larger sized areas of pigmentation. Behind the right posterior molar there are also some irregular areas of a walnut color. There are no localized areas of pigmentation on the inner surfaces of the cheek. There are several small black pinhead-sized areas of pigmentation over the thenar and hypothenar eminences, recently noted by the patient. There are also localized areas of pigmentation upon the glans penis. The pigmentation of the mucous membranes is compatible with Addison's disease, but it is not sufficiently characteristic to be diagnostic.

PRESENT CONDITION OF THE PATIENT

At this time, the condition of the patient is much more characteristic than on the former admission. The melanotic pigmentation has become more marked, and I regard it as especially characteristic upon the palms of the hands, where one sees a marked increase of the pigmentation in the palmar grooves. The pigmentation of the mouth is also quite characteristic now. This pigmentation together with the demonstration of the presence of melanin in the pigment in the skin leaves but little doubt that at present the patient is suffering from Addison's disease. The history of severe gastro-intestinal upset, the markedly low blood pressure, make, together with the pigmentation, a triad of symptoms that could scarcely be explained in any other way than on the basis of Addison's disease of the suprarenal glands. The asthenia, it is true, has been much less marked than is common in most cases. One must assume, I think, that the suprarenal cortex is suffering somewhat less, as yet, than is usual in Addison's disease. The conviction has grown that the symptoms of Addison's disease are not explicable entirely upon the ground of deficiency of the chromaffine system; one must also have more or less

injury to the suprarenal cortex in order that the full-blown picture of Addison's disease may appear. In my opinion, however, the symptoms now present are sufficient for the making of a positive diagnosis of Addison's disease of the suprarenal glands.

NATURE OF THE MALADY

Since Addison's description of the disease in 1855, in which he stated that it was characterized by anemia, bronzing of the skin, digestive disturbances, nervous disturbances, and weakness, leading to cachexia and later to exitus, but little has been added to the clinical symptomatology, though our knowledge of the pathologic-anatomical changes in different cases has grown during the past seventy-five years.

Experience has shown that the onset is insidious, as a rule, and often the first sign is increased fatiguability (both physical and psychical). This is followed by pigmentation of the skin (melanoderma) and of the visible mucous membranes. Gastro-intestinal disturbances are nearly always present in the form of anorexia, nausea, vomiting, and disturbance of the bowel movements. Nervous disturbances of various sorts are prone to occur, including headache, dizziness, fainting attacks, insomnia, neuralgia, and depressive and excited states. The blood pressure is usually very low, and sometimes there is dyspnea, especially on exertion.

The course is chronic, often lasting several years. The progress is, however, usually steadily downward to a fatal termination and toward the end of life the asthenia becomes extreme, and the anorexia more marked; uncontrollable vomiting and diarrhea may develop; the patient becomes delirious and finally comatose before he dies.

The disease is somewhat more common in men than in women and is prone to appear between the twentieth and fortieth years of life. Among the predisposing causes, alcohol, infections, and intoxications of various sorts, traumata, and hereditary tendency have been mentioned.

At *autopsy*, tuberculosis of the suprarenal glands has been found in about 80 per cent of the cases. In other cases, syphilis of the glands, or cirrhosis of the suprarenals, or bilateral atrophy has been found. In a few cases no lesions were found in the suprarenals, though then diseases of the chromaffine system outside of the suprarenal gland have usually been observed.

As you know, the chromaffine system includes the medulla of the suprarenal glands, the paraganglia, the sympathetic ganglia, the glomus caroticum, and the so-called "body of Zuckerkandl." All of these tissues show an affinity for chrome salts in fixing fluids. All of them are derived from the sympathetic nervous system. These tissues produce epinephrine and, normally, they maintain a certain epinephrine content in the blood, which apparently helps to hold the blood pressure at a

normal level and also to maintain the general sympathicotonus of the body. In other words, epinephrine appears to be an endocrine substance made by chromaffine tissues. It also controls the deposits of pigment in the skin and in the mucous membranes; at least, it seems to control the deposition of melanin.

A patient who suffers from Addison's disease has had probably a primary constitutional inferiority of the chromaffine system, which manifests itself as a status thymicolymphaticus in early life. You may recall that in the status thymicolymphaticus there is a tendency to persistence of the thymus. Children with persistent thymus often exhibit suffocation attacks, sometimes dying suddenly during the administration of an anesthetic, during the pulling of a tooth, or during some other simple trauma (so-called *mors thymica*). Such persons, when of the male sex, often exhibit certain feminine characteristics, such as round thighs, broad hips, low position of the umbilicus, delicate clavicles, overextensibility of the elbows, pasty skin, abnormal distribution of the sexual hair, hypotrichosis with transverse crines, female distribution of fat, and gynecomastia. One striking feature of patients with status thymicolymphaticus during early life is a peculiar disproportion in the size of the lateral incisor teeth in the upper jaws contrasted with the medial incisors; for they have very large medial incisors and very small lateral incisors. I notice that this patient exhibits the stigmata of status thymicolymphaticus.

Such a congenital inferiority of the chromaffine system seems to predispose the patient to infections with the germs of tuberculosis and syphilis and with other micro-organisms; moreover, the bacteria seem particularly prone to lodge in the organs of the chromaffine system, especially in the suprarenal glands.

But a constitutional inferiority of the chromaffine system is not sufficient to give rise to the picture of Addison's disease; there must be superimposed upon this congenital inferiority a secondary insufficiency of the chromaffine system and this secondary insufficiency is, as I have said, usually due to tuberculosis, to syphilis, or to some other infectious process or toxic process involving the suprarenal glands or the parts of the chromaffine system outside the suprarenals.

Our patient today over the apices of the lungs on physical examination has signs that make one suspicious. It is possible that he has had an old apical tuberculosis and that, secondary to that, he has developed tuberculosis of the suprarenal glands. One cannot be sure of this, but it is a fairly good guess, since, as I have said, some 80 per cent of the patients with Addison's disease who have outspoken hypo-adrenia are found at autopsy to have such suprarenal tuberculosis. Still, this patient might be among the 20 per cent who do not have tuberculosis of the suprarenals, but who have syphilis, sclerosis, or central atrophy of the suprarenals or of the chromaffine tissue in general.

TREATMENT OF THE PATIENT

The so-called "Muirhead treatment" of Addison's disease consists of the injection of epinephrine daily over a long period. This method of treatment is named after a Dr. Muirhead who himself was a sufferer from the disease. He applied to the Mayo Clinic for treatment and, in consultation with Dr. L. G. Rowntree, of that clinic, this epinephrine treatment was decided upon. Dr. Muirhead himself improved for a long time but, later on, succumbed to the disease.

Recently, attempts have been made at substitution therapy by the use of McLean's suprarenal extract, apparently with at least temporary benefit. It is to be hoped that, before long, we may have suprarenal extracts that contain the important endocrine substances of both the medulla and the cortex of the suprarenals. It is conceivable that emulsions of fresh suprarenal gland, freshly prepared daily and injected subcutaneously or intramuscularly, might be more beneficial than any of the gland extracts thus far employed. I should like to see such an emulsion given a trial.

Attempts to benefit patients suffering from Addison's disease by grafts of healthy suprarenal tissue have already been made by German surgeons. Leschke, on removal of a human kidney because of renal tuberculosis, transplanted a part of the suprarenal gland into the subcutaneous tissue of a patient who had Addison's disease and he believes with benefit. Another German investigator has made a similar graft. It is far too early to be sure of the value of this method of treatment. It does not seem to be probable that the graft would live long, but it is likely that as long as the tissue remains alive, some substances may be given off from it that are valuable for substitutive therapy.

In addition to the substitutive therapy, I should regard as important measures directed toward the overcoming of tuberculous infection and of infection in general. Such measures consist of the administration of vitamins, especially of foods containing vitamin A and vitamin C. Among such foods I would mention cod liver oil and sardines in oil. Tomato juice if given along with sardines in oil will supply practically all varieties of vitamins that have been discovered. Furthermore, any measure that will help to build up the general health and strength of the patient would also help to overcome infection. Of course, when syphilis can be demonstrated to exist, antiluetic therapy should be instituted. The Wassermann reaction in our patient is negative, so it is much more probable that the disease of the suprarenal glands, that we suspect, is, in this patient, tuberculous rather than luetic.

Undernourished patients should be made to gain weight and attempts should also be made to overcome the anemia that accompanies the disease by means of diet, fresh air, sunlight or violet light, and hematinic drugs.

Thus far, we must admit that no satisfactory method of therapy has

been devised for the combating of Addison's disease. The prognosis is, therefore, very grave.

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CLINICAL-PATHOLOGICAL CONFERENCES

FATAL HEMOPTYSIS IN PULMONARY TUBERCULOSIS WITH CAVITY FORMATION IN A PATIENT WHO WAS HOLDING THE DISEASE WELL IN CHECK WHEN THE CATASTROPHE OCCURRED[1]

HEMOPTYSIS is not so very uncommon as a mode of exitus in chronic pulmonary tuberculosis, but in the case here discussed the fatal accident occurred in a patient who apparently was holding the disease well in check when the catastrophe occurred.

The clinical studies of the patient were made by Drs. Rosencrantz and Anderson.

CLINICAL HISTORY

The patient, M. C., a white married woman, twenty-two years of age, was admitted to the San Francisco Hospital on April 16, 1928.

This was her third admission as she had been studied in the same hospital in 1923 and in 1925. At her first admission, she was suffering from shortness of breath, hemoptysis and fatigue; the diagnosis of pulmonary tuberculosis was made. She was treated by means of artificial pneumothorax and was discharged improved.

On her second admission in 1925, she was doing very well, though she had developed pleuropericardial adhesions.

On her admission in April, 1928, she was complaining of cough, weakness, abdominal pains with gas; these symptoms had been rather marked during the preceding six months.

On careful inquiry, it seemed certain that she had suffered from active pulmonary tuberculosis since 1921, when she had pleuritis with bilateral pain. Amenorrhea developed in 1927 and there has been no menstruation since. She had had some burning on micturition early in 1928. Her vision has been poor. She has had deafness in the right ear.

The patient has been of an active type and has been up and about most of the time despite her pulmonary involvement. She weighed most when she was sixteen years of age (146 pounds). Her lowest weight was 86 pounds in February, 1928. She was emaciated on the present entry, the extremities especially showing extreme wasting.

On **physical examination** her temperature was found to vary between 98 and 102 F., and she had never been entirely afebrile during the past year. There was almost no expansion of the chest and there was marked dulness over the upper lobes of both lungs. Amphoric breathing could be heard over the right upper lobe. No breath sounds were audible at the left apex, but there was amphoric breathing below the clavicle on the left and bronchial breathing could be heard at the left base. Bubbling râles were audible throughout both lungs, except over the left upper lobe.

The heart was negative except for gallop rhythm, and occasionally a pleuropericardial friction rub could be heard.

The abdominal walls were held rather rigidly and there was tenderness in the epigastrium and in the right lower quadrant upon deep palpation. The fingers were clubbed. Neurological examination was negative.

[1] Clinical-Pathological Conference at the San Francisco Hospital December 3, 1929.

On **laboratory examination,** the *sputum* contained tubercle bacilli and, at times, elastic fibers. *Blood:* Red blood corpuscles, 2,100,000; hemoglobin, 55 per cent; white blood corpuscles, 5100. Wassermann reaction negative. *Stool* negative for ova, parasites, and tubercle bacilli. *Urine* negative, except for occasional traces of albumin and a few white blood corpuscles.

On ***x*-ray examination,** there were radiolucent areas in both upper lobes with marked opacity below and mottling of the lung fields on both sides, more marked on the right side than on the left; and there was marked pleural thickening over the right lung in its upper part.

Course in the Hospital.—The patient gradually gained 14 pounds in weight after which her weight became stationary and has remained so during the past five months. She continued to have some gastric distress with anorexia and occasional vomiting. The cough and expectoration continued but they became less marked.

At 6.15 A. M. on November 18, 1929, the patient had a sudden and tremendous hemorrhage from the lung and died within a few minutes.

COMMENTS UPON THE DIAGNOSIS (DR. BARKER)

The clinical data placed at my disposal would seem to justify the following diagnostic conclusions:

1. Chronic pulmonary tuberculosis of at least eight years' duration, with extensive infiltration of both lungs (right lung more involved than the left); with intermittent fever, cavity formation in both upper lobes, marked pleural thickening over the upper lobe of the right lung, pleuropericardial adhesions; with cough, dyspnea, persistent sputum, and terminal huge hemoptysis.
2. Marked secondary anemia (red cells 2,100,000, hemoglobin 65 per cent).
3. Myocardiopathy with gallop rhythm.
4. Oral sepsis.
5. Catarrhal gastritis with abdominal pain, tenderness, anorexia, and possibly tuberculosis of the peritoneum.
6. Functional amenorrhea (secondary to the pulmonary tuberculosis and the anemia).
7. Toxic osteoperiostitis (with hippocratic fingers).
8. Deafness of the right ear.
9. Marked undernutrition.

There was no way of saving the life of this patient. The sudden and profuse bleeding from an artery in a large cavity of the lung could in no way be controlled. There was no time for artificial pneumothorax; moreover, the adhesions would have prevented collapse of the lung!

PATHOLOGIC-ANATOMICAL FINDINGS

At the autopsy, made by Dr. Bolin, the main findings were:

1. Tuberculosis, pulmonary, chronic, bilateral, with extensive cavitation in both upper lobes and a smaller cavity in the left lower lobe; with dissemination through the left lower lobe; with hemorrhage from a vessel in the cavity in the right upper lobe; with blood in the bronchi and in the alveoli of both lungs.

2. Tuberculosis, caseous and fibrotic, of the mesenteric and bronchial lymph nodes.

3. Pleuritis, chronic, fibrous, bilateral, with complete obliteration of the right pleura and almost complete obliteration of the left pleura.

4. Pleuropericardial adhesions, chronic, fibrous on the left.

5. Chronic adhesive peritonitis of upper abdomen, characterized by adhesions between liver, peritoneum, stomach, duodenum, and diaphragm, with perisplenitis.

6. Anemia, moderate.

7. Emaciation, moderate.

8. Clubbed fingers.

9. Dental caries and pyorrhea.

10. Simple serous cysts of ovaries.

The sections on microscopical examination show that the cavities are old ones surrounded by a thick fibrous wall with a thin layer of tuberculous granulation tissue lining each cavity. There are no satellite tubercles about these cavities. One cavity is lined by what appears to be flat epithelium and probably represents the smooth-walled cavity of Laënnec. The nodules in the left lower lobe are encapsulated by fibrous tissue. The blood in the alveoli has not produced any reaction in the alveolar walls. The organs are slightly anemic. There is reticuloendothelial hyperplasia of the spleen and lymph nodes. The only really active tuberculous focus is in the mesenteric lymph nodes.

The connection between the abdominal distress in November, 1927 and the peritoneal adhesions is not clear, but there may be a correlation.

The condition of the pleural cavities is perhaps to be correlated with the artificial pneumothorax.

This patient was evidently keeping her lesions in check when the catastrophe occurred.

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CHRONIC FIBROID PULMONARY TUBERCULOSIS WITH CAVITY FORMATION IN ASSOCIATION WITH EXTREME ANTHRACOTIC PNEUMONOCONIOSIS[1]

THIS case illustrates a combination of chronic fibroid tuberculosis with extreme anthracosis in a miner. The marked dyspnea that characterized the case was a clue that gave rise to the assumption of pneumonoconiosis associated with the tuberculosis, particularly when the occupation of the patient is considered.

The clinical studies were made by Drs. Rosencrantz and Mote.

CLINICAL HISTORY

The patient, J. C., an Italian coal miner, age forty-six years, was admitted to the San Francisco Hospital on July 8, 1929, where he remained until he died on November 4, 1929.

The *chief complaints* were of cough with expectoration and marked dyspnea of four months' duration; loss of weight of 33 pounds in the preceding three months; night sweats for two months; and increasing weakness.

Past History.—The patient lived in Italy until he was twenty-nine, after which he lived in America where he worked as a coal miner. There is no history of previous infections, operations or traumata.

Present Illness.—The patient asserted that he had been very well until four months before admission when he began to lose weight, to have cough and night sweats, and to become very short of breath.

On **physical examination,** except for extreme dyspnea, he did not look acutely ill. On percussion, there was marked dulness over both lungs, most marked over the upper lobes. Amphoric breath sounds were audible on the right side in the upper lobe. Expiration was prolonged in the left upper lobe. Showers of râles were audible everywhere over both lungs following cough.

The heart was enlarged to the right and the sounds were distant, but there were no heart murmurs.

On abdominal examination, the liver edge was felt four fingerbreadths below the right costal margin; the surface of the liver was smooth.

There was some clubbing of the tips of the fingers. Neurological examination was negative.

On **laboratory examination,** the *urine* was negative. The *blood* was negative, except for a relative lymphocytosis (34 per cent). The Wassermann reaction was negative. The *sputum* contained tubercle bacilli as well as particles of lung tissue.

Course in the Hospital.—The patient went progressively downhill, continuing to lose weight. He had no appetite and he suffered from severe night sweats. The temperature range was between 99 and 100 F. He died apparently a respiratory death on November 4th.

DISCUSSION OF THE CLINICAL DIAGNOSIS

DR. BARKER: From the clinical data available, we must decide that the patient had chronic pulmonary tuberculosis with cavity formation in the right upper lobe and breaking down of lung tissue, since there were tubercle bacilli and lung tissue in the sputum, and there was,

[1] Clinical-Pathological Conference at the San Francisco Hospital December 3, 1929.

besides, a history of low fever, with loss of weight, cough, dyspnea, night sweats, and gastro-intestinal disturbances. The marked dyspnea and the occupation of the patient as a miner would make anthracosis a probable predisposing cause.

In addition, the patient showed marked undernutrition, a mild secondary anemia, enlargement of the heart to the right, probably due to hypertrophy of the right ventricle because of pulmonary cirrhosis, hepatomegaly and toxic osteoperiostitis, with hippocratic fingers.

DR. ROSENCRANTZ: The students will remember this case very well. We felt confident that there was marked anthracotic pneumonoconiosis on account of the marked dyspnea, and we were sure of the cavity formation and of the existence of pulmonary tuberculosis.

DR. GORDON HEIN: We do not often see pneumonoconiosis on the general medical wards, but it is common to see cases in the tuberculous wards.

DR. LLOYD BRIGGS: I have wondered why some of the pneumonoconiosis cases develop tuberculosis and others do not.

PATHOLOGIC-ANATOMICAL FINDINGS

At the autopsy made by Dr. Bolin, the principal findings were as follows:

1. Pneumonoconiosis (anthracosis), bilateral, marked, with interstitial fibrosis marked (Fig. 23).
2. Pulmonary tuberculosis, chronic, fibroid, with cavitation in right and left upper lobes.
3. Chronic fibrous pleural adhesions, bilateral.
4. Bronchiectasis, bilateral, moderate.
5. Emphysema, bilateral, marked.
6. Hypertrophy of the right ventricle.
7. Clubbed fingers.
8. Anthracosis and fibrosis of the lymph nodes of the hilus of the lung (Fig. 24) as well as of the mediastinal and retroperitoneal lymph nodes.
9. Amyloidosis of spleen (slight).
10. Emaciation.
11. Bronchitis, acute, suppurative.
12. Arteriosclerosis, mild, generalized.

Sections examined microscopically showed slight amyloid infiltration of the malpighian bodies of the spleen. The pulmonary alveoli were filled with hemosiderin-laden phagocytes; there was marked interstitial fibrosis of the lungs, as well as emphysema and great deposits of carbon pigment (Fig. 25).

DR. BARKER: We now possess a method for the recognition of amyloid disease during the life of the patient. By injecting congo red intravenously and determining the amount retained in the blood at the end of one hour one can draw conclusions as to the existence of amyloid-

Fig. 23.—S. A., 29, 178. Pneumokoniosis (anthracosis), fibrosis, and tuberculosis with cavitation (lung).

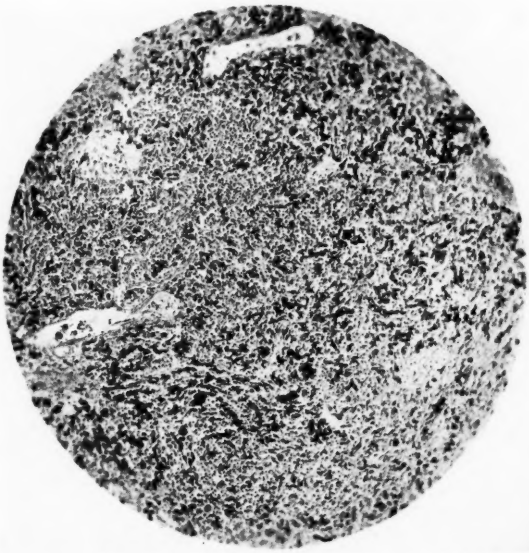

Fig. 24.—S. A., 29, 178. Microphotograph of hilus lymph node showing anthracosis and fibrosis.

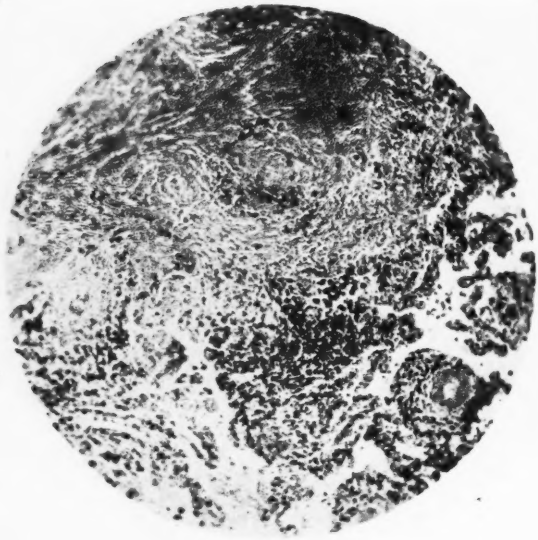

Fig. 25.—S. A., 29, 178. Microphotograph of lung showing anthracosis and fibrosis

osis and its degree. Dr. Howitt is to report on observations with this test at the meeting of the Pacific Interurban Clinical Club.

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PYOPNEUMOTHORAX IN AN ELDERLY ALCOHOLIC, ATHEROSCLEROTIC MAN WITH BRONCHIECTASIS, TUBERCULOSIS, AND MULTIPLE LUNG ABSCESSES[1]

THE next case for discussion at the clinical pathologic conference illustrates well the difficulty of study of patients who have been alcoholic and who enter city hospitals with terminal pulmonary infection. This patient was studied clinically by Drs. Shepardson and Yonan.

SUMMARY OF THE CLINICAL HISTORY

The patient, E. H. C., a white teamster, sixty-three years of age, was admitted to the San Francisco Hospital on November 23, 1929. His *chief complaints* were of difficulty in breathing, weakness, poor appetite, and disturbance of sleep.

Family History.—This was negative, except that one brother and one sister died of pulmonary tuberculosis and one sister died of carcinoma of the bladder.

Past History.—The patient had influenza in 1924, but gave no history of other disease except chronic cough. He had been a heavy drinker throughout life; indeed he had spent much of his money on drink. It was stated that he had had a "chronic cough" for years, which was worse during each winter, and that he had been very nervous, and markedly tremulous, especially during the preceding five years. At one time he had weighed 280 pounds, but during the past three years he had lost much weight; on admission he weighed only about 170 pounds.

One week before admission he had "caught cold" and had felt "pains all over his body." He admitted that he had then taken a "large amount of liquor" and on the following day he became so stiff that he could not walk. He noticed that he was losing his voice and was unable to eat; and he became so sick that he was brought by a friend into the San Francisco Hospital for treatment.

On **physical examination,** his face was flushed, the eyes were glassy, he was breathing heavily and there was a marked tremor of the whole body. He was in an extremely filthy condition and it was difficult to get much out of him on questioning. There was marked emaciation. There were signs of senile dermatitis, especially over the hands, arms, back, and ears. There were multiple lipomata in the scalp and skin. The eyegrounds were negative, and the pupillary reactions were normal.

The lips were dry and showed multiple fissures. The tongue was coated and tremulous. The teeth and gums were in poor condition, showing marked pyorrhea.

The thorax was emphysematous and there was limited expansion of the whole left side with dulness over the whole front and back, on that side; the percussion note was flat over the lower left back. Many râles were audible over both upper lobes in front.

The heart was negative, but there was marked sclerosis of the peripheral arteries. His blood pressure was 110 to 125 systolic; 65 to 80 diastolic. Abdominal examination was negative; on rectal examination the prostate was found to be enlarged, firm, and smooth. There was some clubbing of the fingers. He showed marked emaciation. Scars of varicose ulcers were observable on both legs, and there was a large lipoma in the left upper thigh. The superficial and the deep reflexes were normal.

On **laboratory examination,** the *urine* was free from sugar and albumin, though a few pus cells were present. The *blood* showed a secondary anemia: Red blood cor-

[1] Clinical-Pathological Conference at the San Francisco Hospital December 10, 1929.

puscles, 3,200,000; hemoglobin, 80 per cent; white blood corpuscles, 11,350 with 82 per cent polymorphonuclears. Wassermann reaction negative.

COMMENT BY DR. BRIGGS: When alcoholic patients enter the hospital with pneumonia and other lung complications, they are often difficult to examine. This man was so filthy that the nurses were given a hard task. We were interested in trying to find out why he had lost so much weight.

COMMENT BY DR. SHEPARDSON: The fact that one brother and two sisters had suffered from tuberculosis, made us keep a tuberculous process in mind. We were told that the man had caught cold, that he had had generalized pains a week before entry, and that immediately afterward he had taken a great deal of alcohol. On admission, there were many bubbling râles and ronchi in the lungs, and the resident physician, Dr. Beekler, demonstrated the presence of fluid in the left chest; on puncture this fluid was found to be purulent. The patient exhibited intermittent fever, the temperature rising as high as 102 F., and there was a polymorphonuclear leukocytosis. We felt fairly certain that the patient had pulmonary tuberculosis, with suppurative pleurisy, and that he also had advanced arteriosclerosis. The senile dermatitis did not suggest pellagra. The tumor masses on the head and thigh were taken to be lipomata. His Wassermann reaction was negative. We thought that death was due to the pneumonia or to an empyema following upon a pneumonia in a tubercular patient.

PATHOLOGIC-ANATOMICAL FINDINGS

At the autopsy the main anatomical findings, as reported by Dr. Bolin, were as follows:

1. Pneumonia (bilateral interstitial) with organization, and with multiple abscess formation.
2. Rupture of one lung abscess into the left pleura (Fig. 26), with left pyopneumothorax (the left pleural cavity contained over 3000 cc. of pus, besides air).
3. Moderate bilateral bronchiectasis with staphylococci and streptococci in the contents of the bronchi.
4. Moderate emphysema.
5. Pulmonary tuberculosis in the right upper lobe (with a small cavity) with tuberculosis of the hilar lymph nodes.
6. Acute myeloid reaction in the spleen.
7. Clubbed fingers.
8. Parenchymatous degeneration of the viscera.
9. Moderate glomerulonephritis.
10. Moderate generalized arteriosclerosis with arteriosclerotic changes in the mitral and aortic valves and with calcification of the aortic leaflets.
11. Pyorrhea alveolaris.

12. Lipomata of the scalp and left thigh.
13. Varicose veins (with healed varicose ulcers).

It was Dr. Bolin's opinion that the patient had had a bronchopneumonia of a streptococcal origin, followed by an interstitial pneumonia with organization of the exudate and with multiple abscess formation. One of the abscesses had ruptured through into the diaphragmatic sinus of the pleura and had given rise to a pyopneumothorax with streptococci and staphylococci in the pus. This acute infection was followed by the development of an acute splenic tumor and acute parenchymatous degeneration of the organs. The loss of weight during the past three years may have been connected partly with the old tuberculosis of the right upper lobe, partly with the patient's marked arteriosclerosis, and partly with his chronic alcoholism.

Fig. 26.—Left lung of patient, E. H. C., showing site of rupture of abscess into the pleural cavity, with resulting pyopneumothorax.

COMMENT BY DR. BARKER: Multiple abscesses in the lungs are often viewed as septic infarcts with the development of purulent metastatic pneumonia. Such infarcts tend to lie upon the periphery of the lungs and thus involve the pleura with resulting empyema; one of the abscess cavities actually ruptured in this man and pyopneumothorax developed.

It is interesting that 80 to 90 per cent of all cases of spontaneous

pneumothorax are due to pulmonary tuberculosis; rupture of the lung in pulmonary tuberculosis occurs in men about four times as often as in women. In the remaining 10 to 20 per cent of the cases, spontaneous pneumothorax is secondary to pulmonary gangrene, to trauma, to pulmonary abscess, to bronchiectasis, or to pulmonary emphysema. In rare instances, still other causes may give rise to spontaneous pneumothorax.

The horizontal line of the upper limits of the fluid in the left pleural cavity, as revealed in the roentgenogram, points to the presence of air in the pleural cavity. I suspect that, if this patient had been shaken, a metallic splashing sound might have been audible—the so-called "Hippocratic succussion splash."

Dr. Bolin tells us there was no cirrhosis of the liver in this man though there was some fatty change. It is very interesting that a man could have been alcoholic so long without the development of at least some cirrhosis. Still, many chronic drinkers never develop cirrhosis; evidently the constitutional disposition to cirrhosis hepatis must vary.

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PULMONARY AND GENERAL MILIARY TUBERCULOSIS IN AN INFANT (POSSIBLY ANTENATAL INFECTION; POSSIBLY POSTNATAL PRIMARY SKIN INOCULATION); WITH COMMENTS UPON THE PECULIARITIES OF TUBERCULOUS LESIONS IN THE NONIMMUNIZED[1]

At this clinical pathologic conference there comes up for discussion the case of an infant dead at three and a half months, from generalized miliary caseous foci of tuberculosis, secondary to a primary lesion in the right upper lobe of the lung. There is some evidence in favor of the view that the primary infection was antenatal, though the possibility of primary inoculation of the skin of the buttock after birth must also be kept in mind. The case gives opportunity for brief discussion of the peculiarities of tuberculosis in nonimmunized human beings, since after birth practically every human being becomes gradually more or less immunized toward tuberculosis. The patient was studied clinically by Drs. Riley, Atkinson, Anderson, and Rosencrantz.

SUMMARY OF THE CLINICAL HISTORY

Betty M., a white child, born August 11, 1929, developed within two weeks after birth, a reddish or bluish spot upon the right buttock, which increased in size and, by the end of September, had begun to bleed because the tissues had broken down and ulcerated. A similar spot appeared on the fourth toe of the right foot. The skin lesions were at first thought to be due to hemangiomata and the patient was taken to the University of California Clinic and was afterward admitted to the San Francisco Hospital on October 26, 1929.

The child appeared to be normal except for the areas on the buttocks and on the toe mentioned. The temperature, however, began to rise above 99.5 F. on November 3d and the ulcerated areas increased in size and seemed to be tender.

Physical examination had shown the presence of dulness and of harsh breath sounds in the upper lobe of the right lung. *Roentgenograms of the chest* revealed lesions, apparently tuberculous, in the lungs and the little patient was transferred to the tuberculosis hospital, where she went downhill, developed some meningeal symptoms with retraction of the head and general stiffness. Examination of the cerebrospinal fluid was clinically and microscopically negative. The ulcerated area on the buttock became secondarily infected.

The *blood* showed a leukocytosis of 19,840 with 78 per cent polymorphonuclear neutrophils. The Wassermann reaction was negative and blood cultures were negative. Examinations of the *stool* for tubercle bacilli were negative, but the examination of one slide of *stomach contents* showed bacilli that were acid-fast and that were thought to be tubercle bacilli.

Tuberculin tests made in the ward were equivocal, not definite. Nothing grew from the blood culture, but an antiformin test for tubercle bacilli in the blood was not made.

[1] Clinical-Pathological Conference at the San Francisco Hospital December 17, 1929.

The temperature rose to 101 and then to 103 F. During the last two or three days of life there were patches of slight dulness with tubular breathing discernible over the lungs. The patient became very cyanotic and dyspneic and died on November 26, 1929 at the age of three and a half months.

One clinical question that arose was with regard to the relation of the ulceration of the buttock to the condition in the chest. It was believed that pulmonary tuberculosis and perhaps general miliary tuberculosis existed, though Dr. Bryan, looking at the *x*-ray plates was a little doubtful as to the miliary nodules being tuberculous as they differed somewhat from ordinary miliary tubercules in *x*-ray plates and resembled minute foci of bronchopneumonia, such as he had seen in certain cases of measles.

PATHOLOGIC-ANATOMICAL FINDINGS

At the autopsy made by Dr. Bolin the principal findings were as follows:

1. Primary focus of tuberculosis in the right upper lobe with local caseous bronchopneumonia and with metastases to the hilar lymph nodes (in a nonimmunized person).

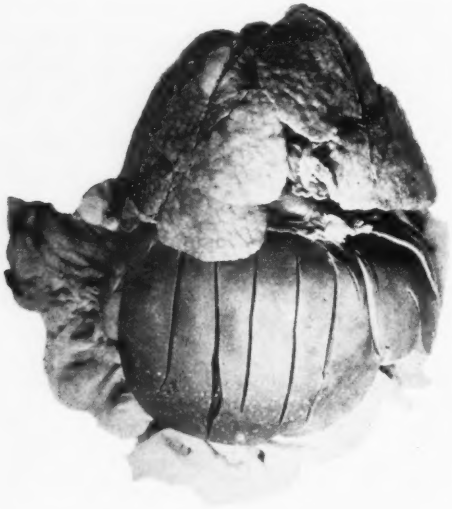

Fig. 27.—Viscera of the child, Betty M., showing miliary distribution of acute caseous tuberculous foci.

2. Miliary caseous foci of tuberculosis in lungs, liver, spleen, lymph nodes, thymus, and meninges with acute reaction surrounding them (Fig. 27).
3. Tuberculous ulcer of right gluteal region.
4. Moderate emaciation.

Commenting upon the findings, Dr. Bolin stated that the child had so-called "angelic facies," with fair skin, and long, curly eyelashes.

The oldest lesion found was caseous pneumonia at the right apex with one pleural adhesion. All the other lesions were younger. There must have been at least two "showers" of tubercle bacilli. The acute reaction surrounding the foci is similar to the reaction following the administration of tuberculin. Each lesion is a small area characterized by a caseated center with a few lymphocytes and plasma cells and with many polymorphonuclear leukocytes about it (Figs. 28, 29). Practically no epithelioid cells are seen and only one giant cell in all the slides.

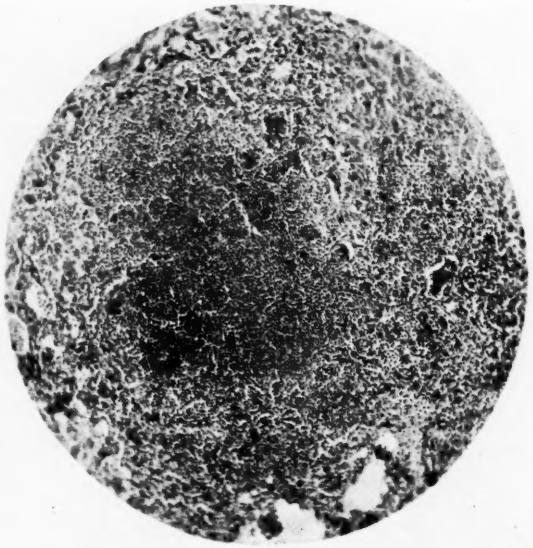

Fig. 28.—S. A., 29, 188. Microphotograph of the lung showing a miliary focus in the lung surrounded by an acute reaction; tubercle bacilli were numerous.

COMMENTS BY DR. BARKER: In the study of tuberculous lesions, it is important to distinguish between *exudative* inflammations and *productive* inflammations.

In *caseous pneumonia* we deal with an exudative inflammation, whereas a *tubercle* is a productive inflammation.

All caseous pneumonia and all tubercles are due to the same tubercle bacillus, though the virulence of the bacillus may vary and the natural and the acquired immunity of the person infected may vary greatly.

Generalized miliary tuberculosis in the adult caused by the spread of

tubercle bacilli through the blood stream, usually gives rise to multiple true tubercles, whereas, in this child, we have to deal less with the true tubercle lesion than with multiple minute caseous foci, associated with marked exudative process in the neighborhood with the presence of many polymorphonuclear leukocytes. Even the roentgenogram of this "miliary tuberculosis" struck the roentgenologist, Dr. Bryan, as being somewhat peculiar, the appearance being slightly different from that of ordinary miliary tuberculosis. That seems to me to have been a very astute observation to have been made during the life of the patient!

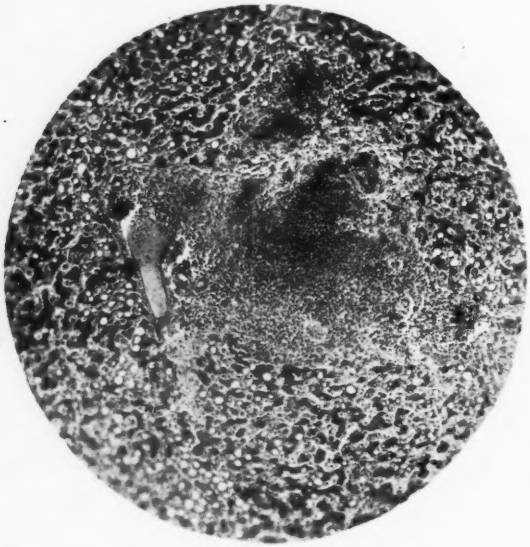

Fig. 29.—S. A., 29, 188. Microphotograph of liver showing acute tuberculous focus surrounded by mononuclears and polynuclears. Tubercle bacilli were numerous.

Dr. Bolin has emphasized the differences in the appearance of tuberculous lesions in the nonimmunized organism and in the immunized organism. The sort of lesion seen in this child is that which is suggestive of lack of immune substances in the organism. From birth on, human beings are gradually more or less immunized to tuberculosis, since we all take in a certain number of tubercle bacilli and gradually acquire a certain immunity. The fact that this child's lesion in the buttock appeared within two weeks after birth is strongly suggestive of antenatal infection. The child has two brothers, one about three years and the other under twenty months old and both of these children yield strong

skin reactions, suggestive of tuberculous infection. It will be important to have the mother of these children examined very carefully for the existence of tuberculosis in her, for it would seem possible that all three children were infected through placental blood. Still antenatal tuberculosis is so extremely rare that we should be very cautious in arriving at a decision between antenatal and postnatal infection. Certainly, the majority of pathologists are very skeptical regarding the occurrence of antenatal infection.

In this patient we did not have to deal with miliary tuberculosis in the ordinary sense of the term, but rather with miliary exudative foci with caseation and marked polymorphonuclear reaction in the neighborhood.

As Dr. Bolin says, in order that the true tubercle may arise with a productive type of inflammation, a certain amount of immunity must have been acquired.

Dr. Bolin feels certain that the primary focus in this child was in the upper lobe of the right lung; that seems to have been the spot where the tubercle bacilli derived from the mother became localized and gave rise to caseous pneumonia. From this primary focus, tubercle bacilli either entered the blood directly or gained access to it through the lymphatic channels, with resulting miliary distribution of the process in the lung, meninges, and other organs. The appearance of one of the miliary foci under the high power may be examined after the clinic.

The possibility of a primary focus in the buttock ought, perhaps, to be kept in mind since French observers have reported primary cutaneous inoculation, as well as primary conjunctival inoculation in nurslings, always associated, however, with caseous tuberculosis of adjacent lymph glands.

The modes of spread of tuberculosis in the body and the several ways in which miliary foci of tuberculosis may appear are well illustrated in the accompanying chart (Fig. 30) that Dr. Bolin has prepared.

There has been much discussion of the significance of primary infections and of disposition upon the origin and course of tuberculosis in human beings. Most human beings who come to autopsy show at least some signs of a preexisting tuberculosis. Most adults yield a positive von Pirquet cutaneous reaction. By far the majority of these have never been ill because of tuberculosis, yet they have all become allergic; they have become sensitized to the virus of tuberculosis. Probably the slight infection that gave rise to this allergy must have exerted at least some protective immunizing influence.

It is interesting that in peoples in which tuberculosis had not been prevalent, the disease when it reaches them occurs in its most severe forms (galloping phthisis; miliary tuberculosis; caseous pneumonia). During the World War this was true among Greeks, Turks, and certain

negro groups; they developed forms of tuberculosis comparable to those met with in nonimmunized animals.

It is interesting, too, that certain infectious diseases (especially measles and influenza) may make the von Pirquet reaction negative when it was positive before (Berlinèr). The frequent development of tuberculosis in persons who have recently had measles or influenza may

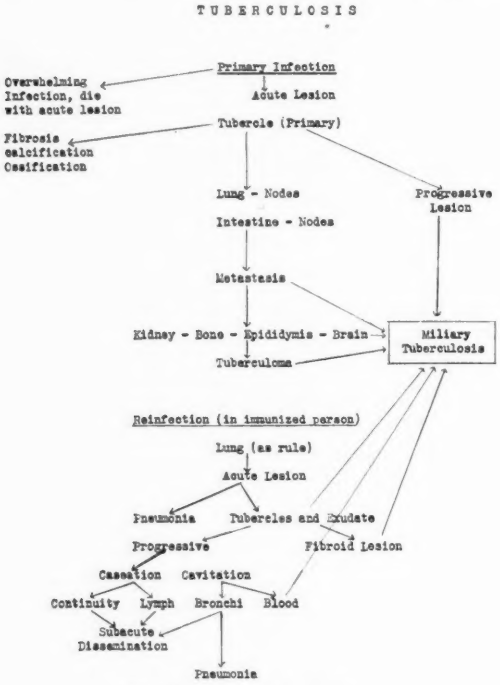

Fig. 30.—Chart of Dr. Bolin.

be related to this change in immunity. The reinfection may have either an endogenous or an exogenous source.

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CHRONIC VALVULAR DISEASE OF THE HEART (DOUBLE MITRAL AND DOUBLE TRICUSPID LESIONS) OF RHEUMATIC ORIGIN, WITH SIGNS OF CARDIAC FAILURE AND WITH PALPABLE SPLEEN[1]

THE varieties of lesions that may be met with in association with cardiac failure are manifold, and it is always interesting to analyze each case on its own merits. The patient to be presented at the staff conference this morning is one of rather unusual interest and merits careful study.

CASE HISTORY

The patient, Mabel A., thirty-five years of age, enters the hospital complaining of shortness of breath and swelling of the abdomen.

Past History.—The patient is married and has kept house. She suffered for some nine months from chorea at the age of eight, the symptoms having been severe. In addition she had diphtheria, whooping cough, measles, and chickenpox in childhood. She had frequent attacks of tonsillitis up to the age of sixteen. At twenty-four she suffered from influenza and this was followed by pleurisy.

At thirty-three a fibroid tumor of the uterus was found; it was treated by *x*-ray and this was followed by premature menopause. The patient has never been pregnant.

Present Illness.—This goes back to the chorea when she was eight years old. It was preceded by pains in the muscles but there was no joint involvement. A physician told her during her choreatic attack that she had "a leaky heart valve." There were no cardiac complaints, however, until she was seventeen, when decompensation first occurred. She became short of breath and there was general anasarca.

At this time she was kept at rest, in bed, for three months. Later, she became stronger and felt very well until twenty-six years of age, when she had a cramplike pain under the right rib margin. The gallbladder was drained and uterine suspension was done. The patient then remained fairly well for four years, when the fibroid of the uterus was discovered and artificial menopause was brought about by *x*-ray treatment.

Last year the patient had an influenzal pneumonia and was in bed for three months. During this time she became decompensated again with general anasarca and marked dyspnea. During the past few months she has been somewhat better, but the abdomen has remained swollen. She entered the hospital for observation and treatment.

Physical Examination.—Marked dyspnea and cyanosis, as well as pallor. Venous pulsation obvious in neck. Chest, barrel shaped; some râles at the bases of the lungs. Heart, markedly enlarged, with palpable diastolic thrill, loud, diffuse diastolic rumble over both the mitral and the tricuspid areas. The aortic second sound was ringing and the pulmonic second sound was accentuated. Heart rate, slow and irregular, suggestive of fibrillation. Blood pressure, 128 systolic, 70 diastolic.

Abdomen, distended with some free fluid in the abdominal cavity. Liver, palpable one hand breadth below costal margin; smooth, firm, tender, not pulsating. Spleen also palpable.

Varicose veins of legs and ankles, dilatation of veins over the back and over the lower abdomen.

[1] Case presented at Conference of Staff of Medical Department at the University of California Medical College, December, 1929.

Laboratory Tests.—*Blood.*—Shows an anemia; red blood corpuscles, 3,710,000; hemoglobin, 77 per cent; white blood corpuscles, 4650, with 55 per cent of polymorphonuclear neutrophils and 38 per cent of small mononuclears. Bleeding time, two minutes; coagulation time, eleven minutes; fragility test normal; platelet count normal.

Stool, negative.

Electrocardiogram showed auricular fibrillation, ventricular rate 55 to 75, wtih marked right axis deviation and inverted T2 and T3.

The patient has been kept at rest in bed, the fluids have been limited; for a period she was placed upon Karrell diet and received digitalis and euphyllin.

DISCUSSION OF THE CLINICAL FINDINGS

DR. KERR: On examination of the patient this morning, I noticed that there was more cyanosis when the patient was lying down than when she was sitting up, that the vessels of the neck were markedly distended, and that the abdominal veins were prominent. The liver edge was down to the umbilicus and the left lobe, as well as the right lobe of the liver, could be palpated. The spleen was palpable, deep in the left flank. There was distinct pulsation in the veins of the arm, and this pulsation was systolic in time. It is interesting that there was more venous dilatation in the left half of the body than in the right. The patient has had an umbilical hernia. The heart shows an enormous area of dulness and a long, diastolic thrill can be palpated maximal to the left of the sternum. The findings make one think of the cases of tricuspid stenosis reported by Dr. Thomas B. Futcher about twenty years ago.

The suggestion has been made that Banti's syndrome should be considered in this patient, because of the palpable spleen and the anemia. Banti's disease would seem to me improbable. The picture is rather that of a very chronic disease of the heart, with double lesions of both the mitral and the tricuspid valves. The possibility of adhesive pericarditis should be kept in mind.

DR. HEIN: In the analysis of the electrocardiogram, I was struck by the marked resemblance to flutter or to the so-called "flutter fibrillation." There are certain runs in the film that look like typical flutter, but, in other parts, there is so much irregularity that one must assume that fibrillation really exists.

DR. ALTHAUSEN: I would suggest that phonograms be taken, as these would be helpful in giving both the pitch and the duration of the several sounds audible. With the new electrical stethoscope supplied by the Western Electric Company, excellent phonograms can be recorded. At the Pacific Interurban Clinical Club meeting here this week the phonographic records of presystolic and protodiastolic gallop rhythms have been most instructive; they were demonstrated by Dr. J. K. Lewis, of the Stanford Hospital.

DR. BARKER: As treatment, this patient has received both digitalis and euphyllin. We know from recent studies of digitalis effects (just

corroborated by Dr. Dock at the Stanford Hospital) that the main benefit in cases like this comes from increasing the cardiac output, not in decreasing the venous flow back to the heart. As Dr. Kerr suggests, Guy's pill or Niemeyer's pill might be especially helpful to this patient.

One cannot help but feel, however, that there will be, on successive breaks, ever increasing difficulty in restoring compensation to a heart as badly damaged as is that of this patient. Sooner or later the time comes when chronic valvular disease of severe grade, associated with myocardiopathy, results in decompensation that cannot be overcome. However, with complete rest, with dietetic measures (including limitation of fluids), with digitalis or strophanthin, and, perhaps, with the help of venesection, some improvement may be gained.

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ARTERIAL HYPERTENSION ASSOCIATED WITH MARKED HYPERTROPHY OF THE MUSCULAR COATS OF THE ARTERIOLES RATHER THAN WITH ARTERIOSCLEROSIS IN A PATIENT WITH SECONDARILY CONTRACTED KIDNEYS[1]

THE case under discussion has many features of interest both to clinicians and to pathologists. It illustrates, on the one hand, the very slow development of renal insufficiency in kidneys that have been undergoing secondary contraction over a long period, probably more than twenty years. On the other hand, it is a striking example of the development of great hypertrophy of the muscular coats of the arteries with maintenance of high blood pressure as a compensatory process in chronic renal disease.

The patient was studied clinically by Drs. Larsen and McCabe, and the autopsy was done by Dr. Bolin.

CLINICAL HISTORY

The patient, R. M., a white American housewife, age thirty-seven years, was admitted to the San Francisco Hospital on August 25, 1929, with the *complaint* of having suffered a violent convulsion followed by pain in the left armpit, weakness of the left arm and difficulty of speech.

Family History.—Her father died of a stroke and her mother of heart failure.

Previous History.—The patient had whooping cough when fifteen months old, scarlet fever, and measles at the age of nine. She had chickenpox at ten. There is a history, also, of what were called "growing pains" with swelling of the ankles at fifteen. Throughout life the patient has had frequent colds and sore throats. She has suffered occasionally from mild headaches. Her menstruation ceased at the age of thirty-one (at the time of her marriage).

Present Illness.—This dates back to 1927, when she began to feel ill and tired and to grow short of breath upon exertion. She consulted a physician who stated that she had many abscessed teeth and advised their removal. This advice was not acted upon, however, until six weeks before admission when the teeth were extracted. After extraction there was much bleeding from the sockets. She awoke one night with partial paralysis of the left hand and inability to speak, suffered a convulsion, went into coma and was brought to the Emergency Hospital for treatment.

On **physical examination,** the patient was found to weigh 120 pounds (having lost 100 pounds gradually during the preceding three years). The face was without expression, the mouth open, the mental state sluggish. The skin was dry and scaly, with maculopapular eruption on the legs, arms, and buttocks. The pupils were dilated but reacted normally. There were no hemorrhages in the eyegrounds but a little exudate was seen in the left retina.

On examination of the chest, the respiratory rate was 18 and there was dulness at both bases, more marked on the left than on the right. A friction rub was heard at the left base in the midaxillary line.

[1] Clinical-Pathological Conference held at the San Francisco Hospital, November 26, 1929.

The pulse rate was 88. The blood pressure was 140 systolic, 95 diastolic. The heart was markedly enlarged, the point of maximal impulse being in the fifth interspace, 13 cm. to the left of the midsternal line. The aortic second sound was accentuated.

In the abdomen, the liver was palpable two fingerbreadths below the costal margin, and there was some tenderness in both upper quadrants on deep pressure.

On rectal examination, there was local inflammation with evidence of a fissure. On vaginal examination, there was retroversion of the uterus and a milky discharge from the cervix.

There was partial paralysis of the left arm and hand. All the deep reflexes, however, were present in all four extremities and were equal on the two sides. Babinski reaction was negative on both sides.

Course in the Hospital.—Examinations by the consulting dermatologists indicated the existence of a "toxic dermatitis." A furuncle developed on each buttock and had to be incised. In early October, the blood pressure rose to 200 systolic and 130 diastolic. At the end of the month the patient became delirious and died on November 1, 1929.

Laboratory Examinations.—Except for a trace of albumin occasionally, the *urine* was reported as negative. The *blood* showed a marked secondary anemia: Red cells 2,780,000, hemoglobin 60 per cent, white blood corpuscles 11,500 with 75 per cent polymorphonuclear neutrophils. The Wassermann reaction was negative.

Renal function test with phenolsulphonephthalein showed complete retention of the dye.

A *Mosenthal test of renal function* showed a range of specific gravity between 1.007 and 1.009; total output for the day was 840 cc., for the night, 765 cc.

Studies of the *blood chemistry* showed extremely high urea-nitrogen and creatinine, the latter rising to 11.1 mg. per 100 cc. of blood.

The *cerebrospinal fluid* was negative with all tests.

DISCUSSION OF THE CLINICAL DIAGNOSIS

DR. BARKER: From the data available on the clinical side, the following diagnosis would seem to be justifiable:

1. Chronic nephropathy with probably secondary contraction of the kidney due to chronic glomerulonephritis; with inability of the kidney to concentrate (hyposthenuria), inability to excrete phthalein, and uremic intoxication with azotemia and creatinemia of high grade and with convulsive seizures, toxic delirium, partial paralysis of left arm and hand, changes in the eyegrounds, and toxic dermatitis.

2. Chronic arterial hypertension (blood pressure, 200 systolic; 130 diastolic), probably a compensatory process for the renal lesions.

3. Dry pleurisy in the upper left chest, with evidence of fluid at both bases, associated with leukocytosis, 11,500, and polymorphonuclear increase 75 per cent.

4. Secondary anemia (red blood corpuscles, 2,780,000; hemoglobin, 60 per cent).

5. Fissura in ano.

6. Retroversion of uterus; endocervicitis; and premature menopause (at the age of thirty-one).

DR. BOLIN: I should like to ask if the clinical examination toward the end of life showed marked increase of fluid in the thorax.

The high content of the blood in creatinine was evidence of a high grade of renal insufficiency. Under normal conditions only 1 to 3 mg. per 100 cc. are present. Five mg. is a high reading and if the creatinine goes above 6 mg. per 100 cc., it is rare to see a patient recover.

DR. LARSEN: The patient became so very ill toward the end that we did not determine precisely the amount of exudate in the serous cavities.

DR. MOFFITT: The disease of the kidneys in this patient possibly could be referred for its origin to some point far back in the patient's life. She has had lesions that have been slowly increasing over a very long period. The etiology in these cases is often very obscure. I am interested in the fact that she had a large number of abscessed teeth extracted shortly before death and that there was much bleeding afterward. It has always been a question in my mind how wise it was to interfere with teeth or other focal infections in advanced renal disease. In such a late stage of the disease, it is doubtful if we do much that is helpful by attempting the removal of focal infections.

PATHOLOGIC-ANATOMICAL FINDINGS

DR. BOLIN: The principal findings at the autopsy were as follows:

1. Chronic glomerular nephritis with marked contraction of kidney (Figs. 31, 32).

2. Hypertrophy of the heart, chiefly of the left side (weight 495 Gm.), with dilatation of both sides of the heart.

3. Hypertrophy of the muscle coat of all arteries (Figs. 33–36).

4. Edema of the lungs, and edema of the pia arachnoid.

5. Increased intracranial pressure characterized by medullary conus.

6. Hydrothorax (left 2000 cc., right 500 cc.), hydropericardium (500 cc.), and ascites (100 cc.).

7. Chronic passive congestion of lungs, liver, brain, spleen, and gastrointestinal tract.

8. Anemia.

9. Cystitis, moderate.

Microscopical examination of the kidneys reveals only two or three hypertrophied normal glomeruli in one whole slide; the rest of the glomeruli are in all stages of fibrosis. Very few glomeruli show the initial changes of a glomerular nephritis; most of them are replaced by fibrous scars. The tubules are usually widely dilated and contain coagulated

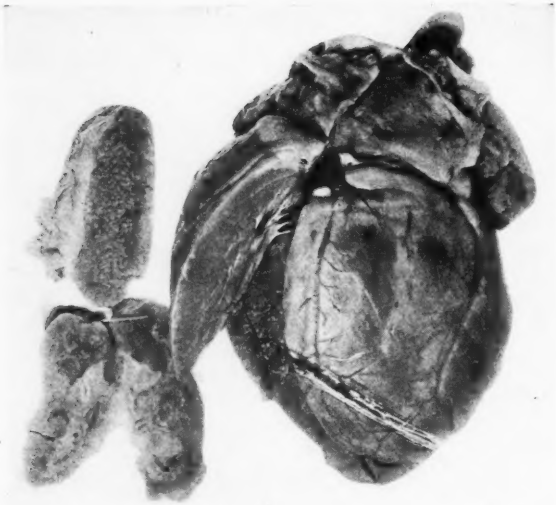

Fig. 31.—S. A., 29, 176. Chronic glomerular nephritis with marked contraction of the kidneys and cardiac hypertrophy. Kidneys weighed 90 Gm.; heart weighed 450 Gm.

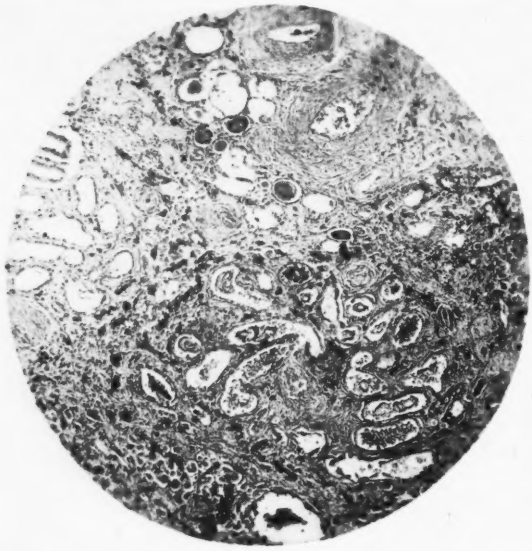

Fig. 32.—S. A., 29, 176. Microphotograph of kidney showing fibrosis of glomeruli, lack of glomeruli, dilatation of tubules and lack of arteriosclerosis in vessels. Note the muscular hypertrophy of the media of the arteries.

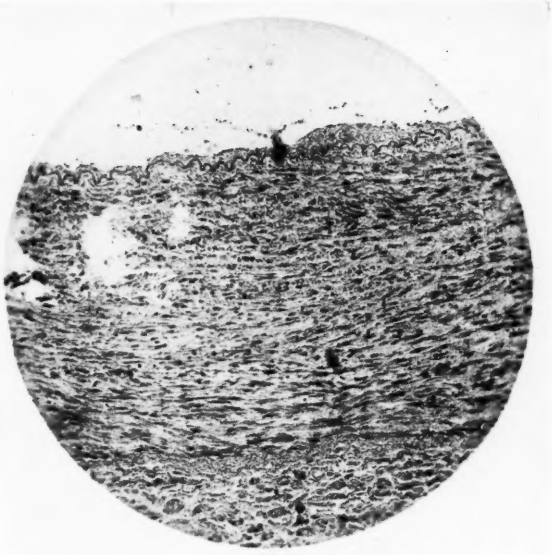

Fig. 33.—S. A., 29, 176. Microphotograph of the wall of the iliac artery. Note the lack of arteriosclerosis and the muscular hypertrophy of the media.

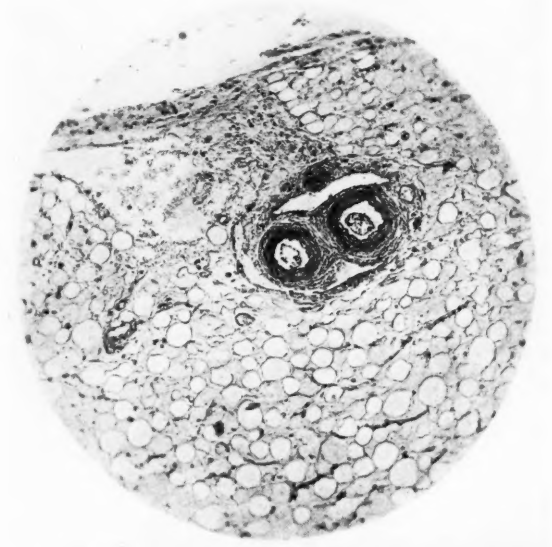

Fig. 34.—S. A., 29, 176. Microphotograph of the periadrenal fat. Note the muscular hypertrophy of the media with the lack of arteriosclerosis.

serum. The tubular epithelium is flat and granular. The interstitial tissue shows a marked chronic inflammatory reaction with fibrosis.

The lesion in practically every arterial wall is a marked hypertrophy of the muscular tunica media. This is seen in the arteries of nearly every organ of the body. Arteriosclerosis is conspicuous by its absence, being seen only in a very early stage in the abdominal aorta and in the coronary arteries.

The heart was of tremendous size, but there were no valvular lesions. It looked as though death might have occurred because of cardiac failure.

DR. BRIGGS: Do you not think that she died a renal death?

Fig. 35.—S. A., 29, 176. Microphotograph of an artery in the pancreas. Note the muscular hypertrophy of the media.

DR. BOLIN: I was inclined to look upon the death as cardiac because of the fluid in all the cavities of the body.

DR. BARKER: It is interesting to speculate as to the actual cause of death; on the one hand, because of the absence of general anascarca, despite the fluid in the serous cavities and, on the other hand, because of the continued rise of blood pressure toward the end. I should have been rather inclined to look upon the death as of uremic origin rather than of cardiac, but doubtless both renal and cardiac insufficiencies played a part.

The astounding feature in this case is the extreme hypertrophy of

the muscular coats of the arterioles with only slight evidences of arteriosclerosis.

In 1852 Dr. George Johnson, in his work on "Diseases of the Kidneys," stated that the walls of the minute renal arteries are usually much thickened in chronic Bright's disease, and that this is due to hypertrophy of their muscular layer. Gull and Sutton, in their celebrated paper on arteriocapillary fibrosis (1872), denied this muscular hypertrophy. We now know that great hypertrophy of the smooth muscle coat may appear in certain cases, and one wonders if Johnson's description may not have been based upon a case in which true hypertrophy of the muscle coat actually was to be seen!

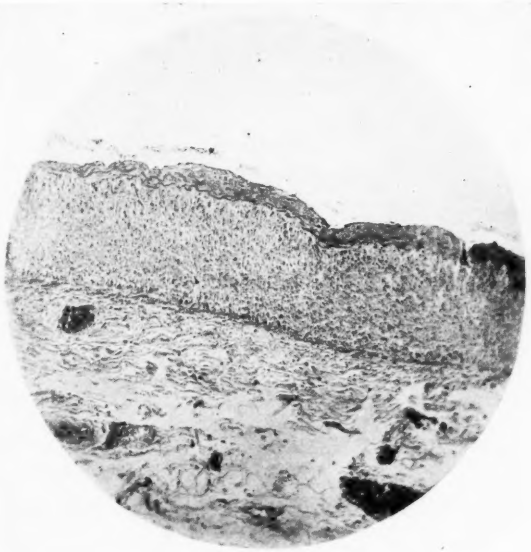

Fig. 36.—S. A., 29, 176. Microphotograph of the mesenteric artery. Note the lack of arteriosclerosis but hypertrophy of the media.

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A FATAL CASE OF PERNICIOUS ANEMIA WITH SUBACUTE COMBINED DEGENERATION OF THE CORD, DEATH BEING DUE TO BRONCHOPNEUMONIA AFTER BEGINNING IMPROVEMENT FROM TREATMENT WITH LIVER EXTRACT[1]

Not all patients recover from pernicious anemia, despite the fact that, through the administration of liver extract, the blood can, in a majority of cases, be brought back to normal. For patients with pernicious anemia are subject to complications and to accidents and the case here reported is illustrative of death occurring after improvement had begun under the influence of liver-extract feeding. The patient was studied clinically at the San Francisco Hospital by Dr. Bruck and Dr. Morris.

CLINICAL HISTORY

The patient, H. C., a white, male clerk, sixty-four years of age, was admitted to the San Francisco Hospital on October 30, 1929. *Complaints:* General weakness and inability to walk.

Past History.—Except for an attack of influenza in 1921, during which he was very ill, and for severe pyorrhea alveolaris leading to the removal of all his teeth four years ago, the patient had been a healthy man until the development of the present illness.

Present Illness.—In February, 1929 (nine months before admission into the San Francisco Hospital), the patient noted that he tired before the end of the day. His physician finding him pale, gave him iron injections and he improved very much for three months; but, subsequently, he grew weak again and about ten days before coming to the hospital, he fainted while at work. He had become so ill that he was unable either to walk or to sit up.

On **physical examination,** he was somewhat overnourished, to the extent of 10 or 15 pounds. Marked pallor; semistuporous; puffy eyelids; sclera tinged, yellowish; pupillary reactions normal; old hemorrhagic areas in both retinae. Lungs negative. Enlarged nodular thyroid, displacing the trachea to the right. Heart somewhat enlarged to the left with soft systolic murmur at the base. Blood pressure, 100 systolic, 40 diastolic. Liver palpable. Spleen palpable two fingerbreadths below the costal margin. Slight edema of the ankles. Abdominal reflexes absent. Positive Babinski on the left. Vibration sense decreased over the lower extremities. Deep muscle sense disturbed in the great toes.

On **laboratory examination,** there was marked anemia. The red blood count was 1,800,000 on admission and had fallen to 920,000 by November 8th, the hemoglobin falling from 35 to 25 per cent, and the color index rising from 1.2 to 1.37. There was no free hydrochloric acid in the stomach juice and the total acidity was from 4 to 6 acidity per cent. No Oppler-Boas bacilli were present and there was no lactic acid in the stomach contents.

Clinical Diagnosis.—Pernicious anemia, with history of occasional epistaxis during the entire course; adenomatous thyroid; subacute combined degeneration of the spinal cord; overnutrition.

[1] Clinical-Pathological Conference at the San Francisco Hospital December 10, 1929.

Treatment.—The patient was given six tubes of liver extract daily, as well as large doses of dilute hydrochloric acid. He was also given a transfusion of blood. At first he rallied markedly, but he soon began to go downhill again and passed into coma, apparently because of an acute pulmonary infection, the respiratory rate having risen to 35, with the appearance of moist râles at the left base. The patient died on November 25, 1929.

PATHOLOGIC-ANATOMICAL FINDINGS

The findings at autopsy have been summarized by Dr. Bolin as follows:

1. Pernicious anemia (characterized by anemia, color of skin, marked hemopoiesis in bone marrow, spleen, liver, lymph nodes, and perirenal fat (Figs. 37–39).

Fig. 37.—S. A., 29, 185. Bone marrow hyperplasia in pernicious anemia, upper femur middle rib, lower vertebra.

2. Pigmentation of liver, spleen, and kidneys.

3. Atrophy of mucosa of stomach with reduction in number of oxyntic cells.

4. Splenomegaly with reticulo-endothelial hyperplasia and myeloid reaction.

5. Degenerative changes in dorsal funiculi of the spinal cord with cavity formation.

6. Residuals of operative incision in left arm (for transfusion).

7. Colloid goiter (substernal) affecting the left lobe.
8. Quiescent tuberculosis of apices of both lungs.
9. Moderate generalized arteriosclerosis.
10. Moderate hypertrophy of the left ventricle.
11. Total loss of all teeth by extraction.
12. Hemorrhage from upper respiratory tract.
13. Bronchopneumonia, left lower lobe.

Sections of the organs, on microscopical examination, show hemopoiesis with normoblasts, megaloblasts, and the myeloid series of cells in the bone marrow, spleen, liver, lymph nodes, and perirenal fat. There

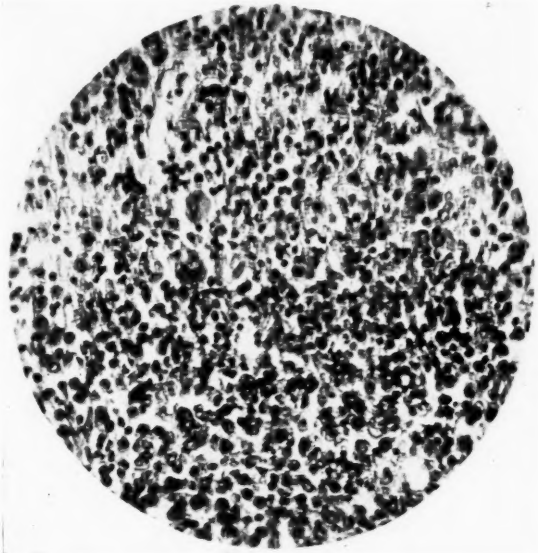

Fig. 38.—S. A., 29, 185. Microphotograph of bone marrow of femur showing hyperplasia.

is an accompanying hyperplasia of the reticulo-endothelial cells in these places. Hemosiderin pigment is found in the spleen, liver, and kidney epithelium. There is phagocytosis of red cells in the spleen and bone marrow. The gastric mucosa shows a flattening of the folds and a marked reduction in the oxyntic cells. There are signs of chronic duodenitis.

COMMENTS BY DR. BARKER: I understand that, in this patient, the platelet count fell to 50,000 per ccm., that there was urobilin in the urine and that, under liver extract, the reticulocyte count went up to 27.6 per cent.

Though we had no data here regarding the determination of megalo-

cytosis during life, I think there can be no doubt that this patient really had pernicious anemia or the so-called "Addison-Biermer" type of anemia. The high grade of anemia with a leukopenia of 2900 and a high color index, together with reduction of the blood platelets, is a very suggestive blood picture, and when it is combined with achylia gastrica and with symptoms and signs referable to subacute combined degeneration of the spinal cord, there can be but little doubt of the diagnosis.

We can feel fairly sure that the anemia in this patient was not wholly of the pernicious-anemia type for he must have had a posthemorrhagic anemia also. He has had epistaxis off and on during the past year and

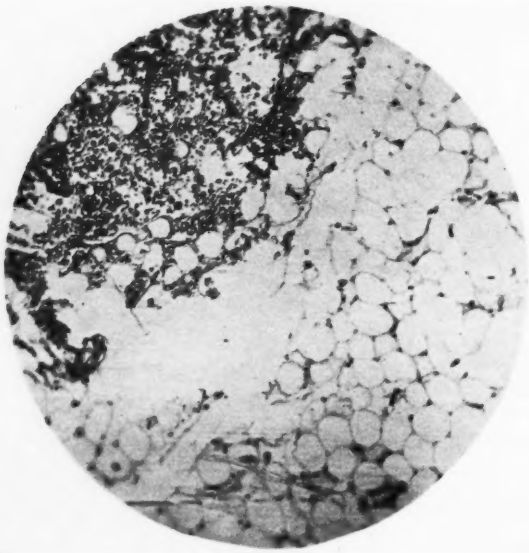

Fig. 39.—S. A., 29, 185. Microphotograph showing hemopoiesis in perirenal fat.

it is reported that he vomited up $\frac{1}{4}$ cupful of blood each morning for ten days at one time. He seems to have had a hemorrhagic tendency, as revealed by this recurrent epistaxis, and it is rather surprising that he did not have more hemorrhages since his platelet count had fallen to 50,000.

Enlargement of the spleen is not so very uncommon in pernicious anemia. It is conceivable, I think, that the large cells of the spleen may have engulfed many of the patient's blood platelets.

I should like to emphasize the importance of paraesthesias of the hands and feet for the early recognition of beginning degeneration of the

dorsal funiculi of the spinal cord. In this patient the vibration sense was also markedly diminished, and that is one of the commonest and earliest disturbances of sensibility in the funicular myelopathy of pernicious anemia. Obviously, the absence of abdominal reflexes and the positive Babinski reaction point to involvement of the pyramidal tract in the lateral funiculi as well.

A patient with pernicious anemia can, of course, develop an infection and die of it, as may any other person. Indeed, it is possible and probable that resistance to infection is diminished because of the anemia. If this patient had not had the ill-luck to develop a bronchopneumonia, it is probable that his blood could have been restored to a normal appearance by continuance of the liver-extract treatment. It would have been important also, of course, to make sure that no more epistaxis occurred. A careful study of the nose might have revealed a bleeding point during times of epistaxis and this could have been successfully treated, perhaps, locally.

Some attention has been paid in the literature to the occurrence of pernicious anemia in association with disease of the thyroid gland. I have here a recent reference to the occurrence of 8 cases of pernicious anemia in association with exophthalmic goiter. The patient today has a colloid goiter, but I should have been inclined to look upon the association as merely accidental. Dr. Briggs tells me that in this hospital there have been cases of severe anemia suggestive of the pernicious type in association with myxedema.

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ACUTE YELLOW ATROPHY WITH BEGINNING TOXIC CIRRHOSIS OF THE LIVER WITH BOTH PORTAL AND BILIARY OBSTRUCTION[1]

THE relation of acute and subacute yellow atrophy of the liver to the development of toxic cirrhosis is beginning to be understood better now than formerly, but we have still much to learn as to the etiology of these conditions, particularly when there is no preceding history of phosphorus poisoning or of arsenic poisoning. The case to be discussed at the Clinical Pathologic Conference today illustrates very well death, from cholemia, of a patient who had had acute necrosis of the liver with jaundice, ascites, and general anasarca.

CASE HISTORY

The patient, Albert F., a white, married man of forty-five, was admitted to the University of California Hospital on June 8, 1929.

His *chief complaints* were: (1) Jaundice of three weeks' duration; (2) edema of the ankles of five days' duration, and (3) distention of the abdomen noticed three days before admission.

Past History.—The man was a machinist, had been married three times, having been divorced twice.

In addition to the ordinary diseases of childhood, he had had malaria at eighteen for which he was treated with quinine. He denied having had venereal diseases, and he had used no alcohol. His average weight had been 145. He had lost weight during his illness (until the edema developed).

Present Illness.—Patient asserted that he had been perfectly well until three weeks before admission, when he lost his appetite, suffered from general malaise, and a few days later noticed that his skin turned yellow and that his stools were of a pasty gray color. The urine also had become very dark. The patient thought that he had had some fever.

Physical Examination.—Drowsy, somewhat short of breath and hoarse. Skin deeply jaundiced. No enlargement of lymph glands. Teeth and gums poorly cared for; pharynx congested.

Ptosis of both eyelids, more marked on the right. Pupillary reactions normal; eyegrounds negative, except for distention of the veins and haziness of the margins of the disks.

In the chest, subcrepitant râles at right base; diaphragm pushed up to the fourth rib on both sides by the fluid in the abdomen.

Heart, not abnormal; blood pressure 130 systolic, 82 diastolic. No arterial thickening.

Moderate distention of the abdomen. No liver dulness elicitable below costal margin. Spleen not palpable. Edema of both lower extremities. All reflexes normal. Rectal examination negative.

Laboratory Tests.—*Blood.*—Red blood corpuscles 4,750,000; hemoglobin 95 per cenlt (Sahli); white blood corpuscles 11,400. Differential count showed 76 per cent poiymorphonuclear neutrophils, 18 per cent small mononuclears, 4 per cent eosinophls, and 2 per cent monocytes.

[1] Clinical-Pathological Conference, University of California Medical School, December 12, 1929.

Urine.—Deep brown color; specific gravity 1.020; contained both bile and sugar. There was also urobilinuria and many granular casts were found in the sediment.

Stool.—Contained no ova or parasites. The icterus index was 190. *Wassermann reaction in the blood*, negative.

Course in the Hospital.—Three days after admission the abdominal distention became so great that the abdomen was tapped and 2200 cc. of fluid removed. The fluid was yellow and turbid, specific gravity 1.008, cell count 164 per c.mm. with 34 per cent of lymphocytes, 60 per cent of epithelial cells, 6 per cent of polymorphonuclear neutrophils, and many red blood corpuscles. No tubercle bacilli could be demonstrated in the fluid. There was 0.5 Gm. of protein per liter in the ascitic fluid. Wassermann reaction in the fluid negative. Examination of the sediment showed no signs of malignancy.

The rose bengal test was not applied because of the deep jaundice. Modified glucose tolerance test yielded a normal result.

The patient was treated symptomatically. His temperature rose before death to 38.4 C.; he became delirious and stuporous and died on the sixth day after admission.

PATHOLOGIC-ANATOMICAL FINDINGS

At the autopsy (made by Dr. J. F. Rinehart, service of Dr. Charles L. Connor) the principal findings were as follows:

1. Acute yellow atrophy of the liver with intense jaundice and diminution in the size of the liver (weight 840 Gm.) with ascites, slight double hydrothorax, hydropericardium, and edema of the lungs; with regenerative hyperplasia of the liver tissue (Fig. 40).
2. Portal obstruction and biliary obstruction due to developing toxic cirrhosis.
3. Pulmonary congestion and edema with intra-alveolar hemorrhage and early bronchopneumonia in lower lobes of both lungs.
4. Parenchymatous degeneration in the kidneys (due to jaundice?) and edema of the kidneys.
5. Reticulo-endothelial hyperplasia in the spleen.

COMMENTS BY DR. BARKER: The liver is an exquisite example of red atrophy. In many areas the liver substance has practically disappeared, the liver cells having been dissolved out and only stroma of blood vessels and phagocytes are left.

The heart was not very large; it weighed only 225 Gm. There was, however, relative insufficiency of the tricuspid valve, as well as dilatation of the right side of the heart.

It was interesting that edema of the legs appeared in this patient before the ascites was noticed.

The presence of sugar in the urine may have been due to the liver disease or to injury to the islands of Langerhans of the pancreas.

Sections of the liver showed a beginning toxic cirrhosis; and this explains why the later test of glucose tolerance did not show deficient carbohydrate function, inasmuch as regeneration of liver cells, perhaps, restored that function, which had earlier been diminished.

It is interesting to speculate on the cause of the toxic necrosis of the liver in this patient. He has had no arsphenamine treatment, nor is there any history of phosphorus poisoning.

It is possible that there are many poisons that can cause this toxic necrosis of the liver. Dr. Kerr has recently found such necrosis in some cases of thyreo-intoxication. Recently, attention here has been called to the frequency of poisoning by cincophen derivatives as a cause of

Fig. 40.—U. A., 29, 58. Subacute yellow atrophy of the liver with regenerative hyperplasia. (Early stage of toxic cirrhosis.)

acute necrosis of the liver. Thus, in one patient, studied by Dr. F. H. Kruse, of San Francisco, three boxes of atophan tablets were taken in the course of several weeks and the picture at autopsy was not unlike that seen in this patient.

It is unfortunate that the jaundice of this patient interfered with the making of the rose bengal test, for in toxic cirrhosis there may be retention of the rose bengal dye in the blood, whereas the carbohydrate tolerance test with insulin may show no marked disturbance of carbohydrate function (owing to the regeneration of the liver substance). It is possible that a part of the jaundice in this case was due to the failure of the newly regenerated liver cells to form connection with bile ducts.

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CHRONIC VASCULAR FORM OF RENAL DISEASE (ARTERIOLAR NEPHROPATHY), WITH FLUID CONTAINING NUMEROUS SMALL MONONUCLEAR CELLS AND OF HIGH SPECIFIC GRAVITY IN THE SEROUS CAVITIES, AND WITH SECONDARY ANEMIA AND TERMINAL INFECTION (QUESTION OF POLYSEROSITIS)[1]

When there is fluid in the main serous cavities (pleural cavities; pericardial sac; peritoneal cavity), we try at once to discover whether we are dealing with a transudate or an exudate. If the fluid has the character of a transudate, we think of a cardiac or of a renal disease, with secondary development of hydrothorax, hydropericardium, and hydroperitoneum. If, on the other hand, the fluid in several serous cavities has the character of an exudate (containing much albumin and being of high specific gravity), we think of the possibility of a chronic polyserositis that may be of tuberculous origin or of still other origin.

In the case under discussion, today, the character of the fluid was during life, suggestive of exudate rather than of transudate, and yet the clinical picture otherwise was that of advanced renal disease with hypertension. Moreover, there were palpable masses in the abdomen that were peculiar and the spleen had become palpable without obvious cause. There were, therefore, several points that were clinically difficult of explanation, but, as usual in fatal cases, the autopsy threw much light upon the things that had puzzled us.

CASE HISTORY

The patient, William B. N., an Irishman, forty-eight years of age, entered the University of California Hospital on October 2, 1929, complaining of swelling of the abdomen, of pain in the left side of the abdomen on stooping, of vomiting in the early morning, and of general weakness.

He had used alcohol habitually, had chewed tobacco, and had suffered from chronic constipation, though he admitted also occasional diarrhea. He had had gonorrhea at twenty-eight, but denied having had syphilis. He had lost some 25 pounds in weight during the preceding three months, but he weighed 180 pounds on admission partly because of generalized edema and of fluid in the serous cavities.

He had stated that his present illness began ten months before admission, when he had "spells of nausea and vomiting, usually after breakfast." Seven months before admission he had noticed left-sided abdominal pain on stooping over, relieved by change in posture. He became weak and confined to his bed and then first noticed that his abdomen was swollen. Some three months ago the abdominal distention became very marked and he began to have edema of the hands and feet.

On **physical examination** the patient was markedly emaciated; there was an icteric tinge to the sclerae, the arteries were sclerotic and tortuous, the cervical glands were

[1] Clinical-Pathological Conference at the University of California Hospital, December, 1929.

slightly enlarged, the breathing was accelerated, and there was evidence of fluid in both pleural cavities, as high as the fifth rib behind.

The heart was slightly enlarged and the sounds were feeble, but there were no murmurs. A pericardial friction rub was heard at one time at the left sternal border. The pulse rate was moderately accelerated. Systolic blood pressure varied between 140 and 200, diastolic between 76 and 110. Venous pulsation was visible in the arms and in the neck. There was marked ascites (with fluctuation wave) and edema of the lower extremities. The liver edge was felt 15 cm. below the costal margin in the middle line and the tip of the spleen was palpable. He had also an enlarged prostate. The eyegrounds were negative except for sclerosis of the retinal arterioles.

On **x-ray examinations**, there was evidence of fluid in the pericardial cavities and in both pleural cavities as well as of collapse of the right lung. The gastro-intestinal *x*-rays were negative.

Laboratory Tests.—*Urine*, diminished in quantity, contained 2 Gm. of protein per liter and many granular and hyaline casts. Phthalein test not satisfactory, but output apparently diminished.

Blood.—Red corpuscles 3,700,000, hemoglobin 58 per cent (Sahli). White blood corpuscles 8800. Differential count, polymorphonuclear neutrophils 76 per cent, small mononuclears 9 per cent, monocytes 6 per cent, myelocytes 5 per cent, eosinophils 3 per cent, basophils 1 per cent. Wassermann negative. Nonprotein nitrogen content of blood serum 65.2 mg. per cent. Icterus index 10.

Ascitic Fluid.—Specific gravity 1.020; almost solid on Esbach test for albumin; numerous red corpuscles and a few white cells present. Guinea-pig inoculation negative. Culture negative.

Pleural Fluid.—Contained 42 Gm. of protein per liter, 110 cells per cubic centimeter, of which 88 per cent were lymphocytes and 17 per cent polymorphonuclears. No tubercle bacilli were found. Cultures were negative.

Pericardial Fluid.—Specific gravity 1.025; 25 Gm. of protein per liter; many cells of which 70 per cent were small mononuclears; no tubercle bacilli found. Culture negative.

Renal function test by Mosenthal's method not satisfactory because of failure of the patient to cooperate.

Liver Function Tests.—With the rose bengal test there was 88 per cent retention after eight minutes and 68 retention after sixteen minutes, showing marked liver damage. With the modified glucose-tolerance test, the first blood sugar was 0.09, the second 0.062, the third 0.105, the fourth 0.052, the fifth 0.033. This indicated a marked hypoglycemia after the injection of insulin, pointing to disturbed carbohydrate function of the liver.

Course in the Hospital.—On November 27th the nonprotein nitrogen in the blood was 67.4 mg. per cent, the creatinine 1.7 mg.

The patient was treated by digitalis, by restriction of fluids and food, by sedatives, by withdrawal of fluids from the abdominal, pleural, and pericardial cavities.

Except for a slight rise of temperature on three different days the patient remained afebrile. His pulse rate ranged between 80 and 120, the respiratory rate between 20 and 35. He had periods of marked diarrhea (stools sometimes blood tinged), associated with low urinary output. Soon after entry he became irrational and disoriented. Though the edema of the extremities cleared up, the ascites continued to be pronounced. After tapping the abdomen, nodular masses were felt in the left lower quadrant repeatedly. The liver remained palpable 15 cm.

below the costal margin and the spleen continued to be palpable. The general course of the patient was downhill.

At a *staff conference* held on November 27th Dr. Kerr pointed out that the patient had shown signs of respiratory infection for several days preceding. On the day before the conference there had been great distention of the peripheral veins, but this did not seem to be due to obstruction within the thorax, such as one sees in mediastinal tumor. Positive venous pulsation had been made out in some of the veins and the liver also was pulsating. The flatness over the chest and the abdomen had increased, indicating an increase in the fluid. The veins in the arms were greatly distended and pulsations could be noted in them as far down as the elbow.

An electrocardiogram made at this time showed some evidence of myocardial change. The T waves were very low, especially in leads 2 and 3. There was also a partial heart block with some dropped beats. The conduction time during certain periods approached two fifths of a second.

Members of the staff at the conference felt sure that there was extensive renal disease with uremic intoxication, marked arteriosclerosis, arterial hypertension, marked enlargement of the heart, myocardial damage, recent pericarditis, tricuspid insufficiency, some liver damage, secondary anemia, and marked chronic passive congestion with dropsical accumulations, and general anasarca. The question of polyserositis came up, but the consensus of opinion was that the fluid in the serous cavities was due to the cardiorenal condition, despite the high content in protein, the high specific gravity, and the large number of small mononuclear cells. Still it was admitted that the man might have a true polyserositis superimposed upon his cardiovascular-renal disease. The pericarditic pseudocirrhosis of Pick was thought of.

The spleen had been palpable and the liver was believed to be enlarged.

The question of possible mediastinal tumor was discussed, as well as the probability of tricuspid insufficiency. Teleroentgenograms showed marked dilatation of the aorta, distention of the left auricle, and a large left ventricle. The prognosis was obviously grave.

Shortly after the conference the patient died.

PATHOLOGIC-ANATOMICAL FINDINGS

Autopsy at 2.30 P. M., 12/3/29 (by Dr. Verne Ross).

The body is that of a wasted male adult, age forty-eight years. The face is drawn, quite cyanotic, and there are prominent veins of the forehead, neck, and chest. A slight exophthalmus with congestion of the conjunctiva is noted.

The nose is negative. The teeth and mouth are coated and dirty.

The subcutaneous tissue of the chest is wasted and in the left infraclavicular region there is a healed scar 3 cm. in length.

The abdomen is greatly distended by fluid. Several midline puncture marks are evidence of previous abdominal taps.

The penis and scrotum are edematous. Decubital ulcers are present on either buttock.

Cn opening the peritoneal cavity by the usual ventral incision, a quantity of greenish-yellow slightly murky fluid escapes. It was estimated that seven to eight liters of fluid were present. Omental fat practically absent. Diaphragm lies at the level of the sixth rib in the midclavicular line on either side; this has pushed the liver downward three to four fingerbreadths below the costal margin.

The two pleural cavities contain equal amounts of clear fluid, estimated at between 1 and 2 liters.

There are fresh fibrinous adhesions loosely binding the lower left lobe of the lung and pericardium to the lateral and anterior chest wall. There are similarly a few adhesions at the base of the right lung.

The heart is enormous; the parietal pericardium is tightly adherent to the diaphragm and shows a rather recent adhesive pericarditis. The heart contains a large quantity of blood and has evidently stopped in diastole. It weighs 745 Gm. The right auricle is greatly dilated and an organizing antemortem thrombus is present in the wall of the auricle. The pulmonary and aortic valves measure 10 and $8\frac{1}{2}$ cm. respectively. The tricuspid valve is large. The heart muscle measures 1.8 cm. at the base of the left ventricle.

The right lung weighs 345 Gm. The upper and middle lobes are normal except for moderate emphysema. The lower lobe is deep-red colored at the base and on section is solid more or less in portions. The left lung weighs 265 Gm. and the upper lobe is normal. The lower lobe shows a similar congestion at the base, with prominent bronchioles on the cut surface, which exude a frothy mucous material.

The bowel is negative, except for its content in scybalous masses.

The tail of the pancreas is quite firm.

The spleen is grayish blue in color and enlarged; it weighs 170 Gm.; on cut surface, the pulp is deep red and solid.

The liver is smooth surfaced, brownish yellow in color and weighs 1300 Gm. It shows a mild passive congestion on the cut surface.

The suprarenal bodies are normal and together weigh 24 Gm.

The stomach is greatly distended by gas. The mucosal surface is negative. The duodenum is also negative and the ampulla of Vater patent.

The gallbladder is thick walled and measures 8 cm. in length; it contains no stones.

The left kidney is normal in size and position; the ureter is normal but somewhat bound down to adjacent structures. This kidney weighs 130

Gm. The true capsule strips with difficulty (Figs. 41, 42) and leaves a uniformly, roughly granular surface having a grayish color, intermediate between a red and a pale granular kidney. On longitudinal section the glomeruli stand out very prominently as minute translucent bodies against a grayish background. The cortex is ill defined and measures approximately ½ cm. in thickness (Fig. 43).

The right kidney weighs 120 Gm. and is quite similar in all respects to the left.

Fig. 41.—Uniformly contracted kidney with marked pitting of the surface and a moderately adherent capsule. This shows an unusual degree of damage for an arteriolar sclerotic kidney.

The bladder is negative. The prostate is small and normal. The seminal vesicles on either side contain a number of hard yellowish-white concretions measuring up to 8/10 cm. in diameter.

The aorta is less sclerosed than many of the other vessels. It contains numerous atheromatous plaques but no hard areas of calcium deposition.

Microscopical Examinations.—*Lungs.*—Sections of the lower lobes show thickening and collapse of the alveolar walls. Heart failure cells, loaded with light brown pigment, are numerous in the collapsed alveoli. The vessels show sclerosis and thickening of their walls and are mostly congested.

Sections of the upper lobes show evidence of passive congestion in

Fig. 42.—Another view of same kidney shown in Fig. 41.

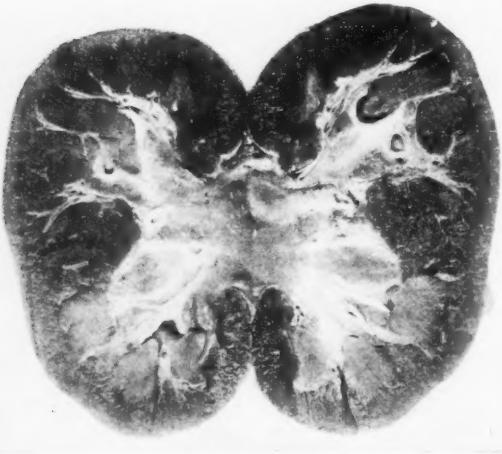

Fig. 43.—The cut surface shows a uniform narrowing of the cortex and many small scars scattered throughout.

some areas with areas of compensatory emphysema. Heart failure cells are numerous. The pleural surface is quite edematous and a thin layer of fibrin is adherent to the surface.

Heart.—Section of the right auricle shows a thickened epicardium, composed of newly formed vascular connective tissue with adherent plaques of fibrin and supporting numerous pigment cells similar to those seen in the lung. The auricular muscle is infarcted, probably following thrombosis of a vessel. The muscle bundles are separated, pale, and swollen. Adherent to the endocardium and enmeshed in the trabeculae carneae is a large antemortem thrombus consisting of densely packed red blood cells, fibrin, and masses of platelets and scattered leukocytes. The ventricular muscle shows degenerative changes in the form of

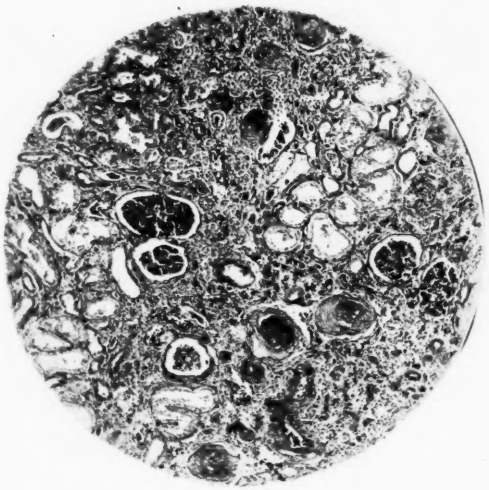

Fig. 44.—The photomicrograph shows sclerosis of many glomeruli, partial or complete, and marked thickening of the walls of arterioles. There is sclerosis of the larger arteries also similar changes in the arterioles throughout the body.

clouding of the fibers with separation. Some of the bundles cut transversely show edema.

Aorta.—Sections of the aorta show some thickening of the intima. Between the media and intima are areas of degeneration and fatty infiltration.

Liver.—The liver shows the effects of long-standing passive congestion, which is manifested by a condition of collapse induration about the central veins. In these areas the liver cells have dissolved and the stroma is collapsed with a few scattered red blood cells to be seen. There is no excess of pigmentation.

Spleen.—Sections show a moderate congestion of the large sinusoids.

The small arteries, as well as the larger-sized ones, show a remarkable degree of sclerosis, with narrowing of their lumina.

Kidneys.—Many glomeruli show hyalinization of the capsular wall. In some, this process has included the whole glomerulus, or in other cases a part of it, so that the glomerular tuft is much shrunken in size. Others show thickening and hyalinization of the capsular space and hemorrhage into the glomerular tuft, without other demonstrable changes. The vessels are markedly sclerotic and many of the arterioles in relation to the glomeruli have practically no lumen (Fig. 44). There is a marked fibrosis about some of the glomeruli, with a diffuse cellular infiltration, mostly lymphocytes. These changes are most pronounced in the cortical area.

Lobules of convoluted tubules stand out in relief grouped about the glomerular areas. There is definite edema with irregular tubular outlines. The cytoplasm of the lining cells is granular and stains a deep pink. In many the nuclei are indistinct or absent, and there is an albuminous precipitate within many of the lumina. This does not represent post-mortem degeneration.

Adrenals.—In a section of one of the adrenals is an island of white blood cells, which are apparently of the lymphocytic series. The adrenals are in no other way remarkable.

Prostate.—Sections of the prostate show a mild degree of glandular hyperplasia.

Pathologic-anatomical Diagnosis.—Essential hypertension with vascular (arteriolar) renal disease. Chronic adhesive pericarditis and myocarditis with heart failure. Atelectasis of both lower lobes of lungs. Generalized edema and anasarca. Chronic passive congestion of the viscera.

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CEREBRAL HEMORRHAGE CAUSING LEFT HEMIPLEGIA IN A SENILE PARAPARETIC PATIENT WITH EXTENSIVE GENERALIZED ARTERIOSCLEROSIS[1]

THE patient, J. M., an Irishman seventy-four years of age, occupation track oiler, was admitted to the San Francisco Hospital October 12, 1929 in a semicomatose condition so that the history had to be obtained from his son. The clinical studies were made by Drs. Briggs, Shepardson, and Goodman.

Owing to age, he stopped work some six years ago although he had been quite well for the past fifteen years. On the afternoon of October 9th (three days before admission) he had seemed quite normal but was found on the landing of a stairway where he had fallen. Carried to bed he was able to speak and his son thought him to be still quite rational. On the following afternoon he was seen again by his son who said that he appeared to be practically unconscious, occupying the same position in bed in which he had been placed the night before.

Aside from a peculiar broad-based, shuffling gait (not stamping), which had been noticeable for five to six years, the patient's strength, mentality and general health had apparently been satisfactory.

On **physical examination** in the hospital (Drs. Shepardson, Goodman, and Cohn) he was described as semicomatose, markedly emaciated, and dehydrated. Although he responded to questions with feeble "Yes" and "No" answers and was quite hoarse, he was evidently irrational.

There was a marked arcus senilis. The pupils were equal, though small, and they reacted normally. No impairment of extra-ocular movements. In the eyegrounds the vessels were tortuous and showed a silver wire appearance. No choked disks. Corneal reflexes bilaterally sluggish. Tone of the masseter muscle less on the left than on the right. Left nasolabial smoothed out; left cheek flapped with respiration, but forehead was symetrically wrinkled and tonus was good in both closing muscles of the eyelid. Palate was pulled to the right; tongue not quite in middle line. Left eardrum perforated with retraction. Markedly carious teeth. Slight rigidity of neck. Cheynes-Stokes respiration, but lungs clear on auscultation and percussion. Heart slightly enlarged to the left. Increased dulness over aorta. Pulse rate, 85 with numerous premature beats. Blood pressure 130 to 122 systolic; 70 diastolic. Systolic level of blood pressure irregular, but not a pulsus alternans. Peripheral arteries markedly tortuous with palpable beading.

Abdomen scaphoid. Liver and spleen not palpable.

Left upper extremity relatively flaccid, without evidence of voluntary motion. Right upper extremity somewhat hypertonic and moved about aimlessly. Deep reflexes in left upper extremity, markedly hyperactive and Hoffman sign positive. Deep reflexes in right upper extremity hyperactive. Abdominal and cremasteric reflexes not elicited.

No evidence of voluntary movement in either lower extremity. Hypertonus on the left, knee jerks hyperactive on both sides. Ankle jerks less active. Bilaterally positive Babinski.

Genitals negative. On rectal examination, prostate slightly enlarged but otherwise normal. The Emergency Hospital reports that when the patient was there he was able to move the right leg but not the left.

Laboratory Tests.—*Blood.*—White blood cells 41,000 with polymorphonuclear neutrophil leukocytes 76 per cent. Icterus index 25, van den Bergh's test yielded an

[1] Clinical-Pathological Conference, San Francisco Hospital, November 26, 1929.

immediate, direct, positive reaction. On quantitative examination there were 30 mg. of bilirubin per liter (6 units); urea 84 mg. per cent. Wassermann negative.

Urine showed a trace of albumin; otherwise negative.

On *lumbar puncture* the pressure of the cerebrospinal fluid was not increased; 240 red blood corpuscles per cubic millimeter (probably traumatic in origin); faint xanthochromia; Pandy 2 plus.

Course in the Hospital.—The patient continued to have Cheyne-Stokes respiration at intervals. The temperature rose to 102 F. on October 13th and coarse, moist râles appeared at both bases with some impairment of the percussion note on the left.

On October 14th the patient showed rectal sphincter incontinence. On October 15th he passed into deep coma, without change in the neurological signs. He died on October 16th.

Comment by Dr. Barker Upon the Clinical Diagnosis: That this patient suffered from some form of severe cerebral insult on October 9th would seem clear, and there was some evidence of increasing cerebral involvement upon the following day. The high degree of arteriosclerosis present (beaded peripheral arteries, retinal arteriosclerosis, double arcus senilis, cardiac changes) naturally led one to refer the cerebral insult to vascular lesions, either hemorrhage or thrombosis. The very sudden onset is suggestive of apoplexy from hemorrhage rather than of thrombosis. Because of deep coma and Cheyne-Stokes respiration one would expect an extensive cerebral involvement rather than a minor lesion. On account of the history of broad-based, shuffling gait for several years past, one wonders if the patient may not have had a senile paraparesis upon a cerebral arteriosclerotic basis for many years; upon this the recent ictus may have been superimposed.

The fact that in the Emergency Hospital there was spontaneous movement of the right side of the body and that since admission to this hospital there have been some aimless movements of the right upper extremity, whereas no spontaneous movements on the left side of the body have been observed and this left side is relatively flaccid (despite the hyperactive deep reflexes) would make it seem probable that whatever happened on October 9th caused a severe left-sided hemiplegia. We can be sure, however, that both pyramidal tracts have been injured because of the bilateral Babinski reaction, the hyperactive deep reflexes on both sides, and the entirely absent cremasteric and abdominal reflexes on both sides. Whether the right hemiparesis is due to the lesions occurring on the date of his fall, October 9th, or to some earlier lesion, one could not be sure. When there is bilateral hemiplegia, without involvement of the upper facial on either side one can feel sure that the lesions are somewhere above the level of the facial nerve nuclei in the pons. Bilateral hemiplegias are not infrequently due to pontine or midbrain lesions involving both pyramidal tracts, but the profound disturbance of consciousness in this case would make one feel that the lesion must be higher up, somewhere in the cerebral hemisphere and most probably, of course, in the region of the internal capsule. Hemorrhage in the region

of the right internal capsule could have caused the recent left hemiplegia; the right hemiparesis could be caused by a lesion involving the pyramidal tract on the left side anywhere between the motor cortex and the upper pons. A large hemorrhage in the neighborhood of the right internal capsule with perhaps rupture into the ventricle could account for the profound disturbance of consciouness and the Cheyne-Stokes breathing.

Of course one could think of a widespread meningeal hemorrhage (subdural or subarachnoid) but it would seem scarcely likely that such a meningeal hemorrhage could cause so widespread (and bilateral) paralysis. The physician who made the lumbar puncture was inclined to think that the blood found in the cerebrospinal fluid was due to the puncture itself and not to the earlier presence of blood in the fluid. It must be admitted, however, that the slight xanthochromia present is suggestive of some earlier blood in the subarachnoid space. Bilateral cerebral thrombosis in a man of this age with generalized arteriosclerosis would not be surprising, but the abrupt onset and the fact that the blood pressure was not very low are points favoring the idea of cerebral hemorrhage rather than thrombosis.

Of course certain other conditions must be thought of as possible causes of the clinical symptoms and signs. For example, epidemic cerebrospinal meningitis appearing in an old man, or epidemic encephalitis, could cause such a picture. The leukocytosis of 41,000 cells with 76 per cent lymphocytes is compatible with the idea of meningitis or encephalitis, but it could also be due to cerebral hemorrhage. There was slight rigidity of the neck, but this was not outspoken and I am told that Kernig's sign was not elicited.

The occurrence of jaundice with the cerebral insult makes one think of the clinical picture described by Guillain, of Paris, under the title, "Icterus and Meningeal Syndrome with Polynucleosis." I do not recall, however, having seen any case before that could correspond to Guillain's syndrome.

The cause of the jaundice in this patient is not entirely clear. Of course, hemolysis after hemorrhage might be responsible, but one has to think also of the possibility of some local condition in the liver, gallbladder, or biliary passages.

As to the cardiac condition, there has been tachycardia and arhythmia with premature beats. The heart is enlarged and systolic contractions evidently varied in strength from beat to beat. With the high degree of general arteriosclerosis present it would seem likely that there has been coronary sclerosis with myocardial injury.

It is almost certain, too, that in this patient there must have been arteriosclerotic changes in the kidney. Albumin was present in the urine, though casts were apparently not observed. There was, however, some renal insufficiency, as shown by the azotemia. On admission there were 84 mg. of urea nitrogen per 100 cc. of blood and Dr. Briggs tells me

that before death the urea nitrogen amounted to as much as 284 mg. per 100 cc. It is not likely, however, that this uremic state was responsible for the paralysis or for the coma. I should think that it probably developed as a terminal feature because of failing heart and of poorer circulation in the kidney already impaired by arteriosclerotic change.

The oral sepsis is interesting, in passing, but probably stands in no direct relation to the main clinical features of the case.

The appearance of râles at the bases and of impairment of the percussion note during the last few days of the man's illness suggests the development of terminal hypostatic pneumonia.

In summary, then, it would seem to me that the clinical history points to:

1. General and cerebral arteriosclerosis with recent hemorrhage in the right side of the brain, causing left hemiplegia and some lesions, either simultaneous or earlier in the left side of the brain, causing right hemiparesis, the coma, and the Cheyne-Stokes respiration probably being due to the right-sided cerebral hemorrhage of October 9th.

2. Arteriosclerotic cardiopathy with coronary sclerosis and myocardial scarring with heart hypertrophy, premature beats, and contractions of varying strength.

3. Arteriosclerotic renal disease with renal insufficiency and terminal, high-grade azotemia.

4. Oral sepsis.

5. Jaundice (of unclear etiology, possibly hemolytic).

6. Terminal hypostatic pneumonia.

I shall be very much interested in hearing what was actually found at autopsy.

SUMMARY OF PATHOLOGIC-ANATOMICAL REPORT BY DR. BOLIN

The principal findings at autopsy were as follows:

1. Arteriosclerosis, marked, generalized, involving chiefly the heart valves (aortic and mitral), the aorta, the coronary arteries, the mesenteric arteries, the iliac arteries, the splenic arteries, the peripheral arteries, and the cerebral arteries.

2. Cerebral hemorrhage on an arteriosclerotic basis about the right basal ganglia and internal capsule.

3. Hypertrophy of the left heart and dilatation of both ventricles.

4. Bronchopneumonia, right lower lobe.

5. Arteriosclerotic nephropathy.

6. Pulmonary emphysema.

7. Arcus senilis.

8. Unequal pupils.

9. Atrophy of the liver and appendix.

10. Dental caries and pyorrhea.

11. Leukoderma of penis and scrotum.

12. Calcified costal cartilages.
13. Hypertrophy of prostate (moderate).

The microscopical examination of the sections from the brain show sclerotic vessels, some cortical atrophy, corpora amylacea, pigmentation of the cells and patchy gliosis.

The sections of the testes show spermatogenesis still going on.

The prostate slides show muscular hypertrophy.

The pituitary body shows a slight fibrosis of the anterior lobe.

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LEFT HEMIPLEGIA FOLLOWING UPON ARTERIOTHROMBOSIS DUE TO OPERATION FOR REMOVAL OF AN ENDOTHELIOMATOUS MASS IN THE RIGHT SIDE OF THE NECK[1]

THE case under discussion illustrates, in the first place, the occurrence of a rare tumor in a lymph gland of the neck and, in the second place, the serious consequences that may result from ligation of the common carotid artery at operation for the removal of such a tumor. The patient was studied clinically by Drs. Kilgore and Yonan.

CLINICAL HISTORY

The patient, E. R., a white male, sixty years of age, was admitted to the San Francisco Hospital on July 10, 1929, with the *complaint* of a discharging wound in the right neck that had persisted for four months following upon the removal of a tumor on March 26, 1929.

The patient dates the *onset* of his present malady to an automobile accident that occurred in 1927, in which his face was bruised and he was incapacitated for several weeks. During convalescence, he noticed a small mass in the right side of his neck, just below the angle of the jaw. This mass increased in size gradually until March, 1929, when it was 3 inches in diameter, flat, and firm, but not attached to the skin. It caused only moderate discomfort. Though he had no severe pain, he consulted a physician who operated upon the neck, removing the mass; but after the operation, the wound remained open and gave off a foul discharge. During the next four months, the patient felt pain in the right shoulder especially on movement of the arm. He had also a right-sided temporal headache, requiring medicine for its relief.

On **physical examination,** a suppurating postoperative wound was found below the jaw on the right side and, on palpation, a hard mass, some 2 inches in diameter, rather tender on pressure, could be made out. It was attached to both the superficial and the deep tissues and was fixed. Below this mass, another could be felt extending down to the clavicle. There was no enlargement of the glands in either triangle of the neck. Physical examination was otherwise negative. There was no anemia. The Wassermann reaction was negative.

Operation.—On July 31, 1929, Dr. Kilgore undertook a radical dissection of the right side of the neck, during which it was found that the tumor mass was firmly bound to the vessels and it became necessary to ligate the common carotid artery. A few days after the operation, the patient gradually developed paralysis of the whole left side of the body and became drowsy and stuporous. He slowly went downhill and died on October 28, 1929.

COMMENTS ON THE DIAGNOSIS (DR. BARKER): We are asked to make a diagnosis here without knowledge of the histologic findings in the tumor that was removed. Of course, the commonest masses in connection with lymph glands in the neck, are due to tuberculous or luetic inflammation or to Hodgkin's disease. Primary tumors of the lymph

[1] Clinical-Pathological Conference at the San Francisco Hospital December 10, 1929.

glands of the neck are very uncommon, though secondary tumors are quite common. In this case, there is no history of a primary tumor elsewhere. At the same time, we must look upon this mass as having been due to a malignant growth, for otherwise there would not have been a second operation of such magnitude.

In the absence of any evidence of a primary tumor elsewhere, we should have to think, I suppose, of a primary tumor originating in the right side of the neck. If it arose in the lymph gland, one would have to think of a lymphoma or of a lymphosarcoma since other primary malignant tumors there are very rare.

There is one condition that should, of course, be thought of. It is possible that the tumor did not arise in a lymph gland in the neck, but instead arose in some other structure. When a growth arises in the upper part of the neck below the ear and near the angle of the jaw, I always think of the possibility of an origin from the so-called "carotid gland" or glomus caroticum. These tumors, though they are rare, occur occasionally. This carotid gland is a part of the chromaffine system; and normally it is only a few millimeters in diameter and weighs only about 50 mg. It is oval in shape and lies at the angle of bifurcation of the common carotid artery. It contains sympathetic ganglion cells and fibers and also chromaffine cells, that is to say, cells that stain deeply with bichromate of potash. When a tumor arises in this gland, the tissue of the new growth is very much like that of the normal organ. One sees heaps of alveolar cells that stand in close relation to the capillaries and, on histologic examination, the tyro is apt to think that he is dealing with a "perithelioma," but one can sometimes demonstrate the chromaffine nature of some of the tumor cells. One should always be on the lookout for this kind of a tumor when a mass develops in the area between the lobule of the ear and the larynx. It is said to occur more often on the left side than on the right, and in men more often than in women. If it is removed, it usually does not recur and it does not form metastases. It is very difficult to remove surgically because of its close relation to the carotid artery and to the vagus nerve. This form of tumor has been carefully described by Beitzke, who speaks of "struma of the glomus caroticum." There is a very good review of the literature on the subject in W. Gronemann's article in Virchow's Archiv for 1914, Volume ccxviii, 163–170.

PATHOLOGIC-ANATOMICAL FINDINGS

At the biopsy of the tissue removed and at the autopsy made by Dr. Bolin, the principal findings were:

1. Endothelioma arising in the cervical lymph nodes of the right side; removed by radical neck dissection with ligation of common carotids.

2. Partly healed operative incision on right side of neck with induration and tumor formation.

3. Thrombosis of right internal carotid artery extending up to the circle of Willis and into the right middle cerebral artery.
4. Anemic infarct of the cerebrum involving the right basal ganglia and up to the right cerebrum into the right frontal lobe.
5. Necrosis of tip of right ear.
6. Unequal pupils.
7. Bronchopneumonia both lower lobes.
8. Mild arteriosclerosis of aorta and kidney.
9. Emphysema of lungs.
10. Atrophic appendix.
11. Dental caries.

The surgical specimen, which had been removed previously, consisted of a block of tissue measuring 12 by 8 by 4 cm. It consisted of skin, subcutaneous tissue, muscle, lymph nodes infiltrated with tumor, and the carotid vessels. The jugular vein was absent. The tumor mass invaded the nodes and extended about the vessels. Sections of the tumor showed it to be composed of round and spindle-shaped cells. The cytoplasm was clear and lightly staining. The nucleus of these cells was large and vesicular with several nucleoli. There was no pattern except a column-like structure. In places, channels and pseudochannels were forming. It seemed to arise from the sinus endothelium of the nodes, although this was not at all certain. The diagnosis was a combined clinical and pathologic one, based on the lack of a primary tumor and the cellular appearance of the lymph-node tumor.

On microscopical examination of tissues, no metastases could be found in the slides. Apart from a mild arteriosclerosis of the kidney and the bronchopneumonia, the findings in these slides were not important.

COMMENT BY DR. CALLANDER: I believe that the first ligation of the common carotid artery was done in this city by Dr. Levi Lane. The mortality after ligation of the common carotid is rather high, so that it is always a formidable operation, though when it is done for aneurysm the results are better than when no aneurysm is present.

COMMENT BY DR. BARKER: The slow onset of the paralysis after the operation was suggestive of thrombosis extending upward into the arteries of the cerebrum, with anemic necrosis of the brain, especially in the domain of distribution of the middle cerebral artery. I should think it worth while to examine sections of the tumor of the neck for chromaffine cells, since endothelioma might arise in the glomus caroticum as well as in a lymph gland.

COMMENT BY DR. BOLIN: An excellent history of the whole subject of endothelioma will be found in Ewing's book on the Neoplastic Diseases. I am of the impression that the endothelioma in this patient arose from the endothelial lining of a lymph sinus in the lymph gland in the right side of the neck.

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TERMINAL BRONCHOPNEUMONIA IN AN OBESE ATHEROSCLEROTIC DRUNKARD WHO, DURING LIFE, SHOWED SIGNS OF PERIPHERAL NEURITIS AND OF A HALLUCINATORY PSYCHOSIS[1]

A COMMON form of ending of the life of a drunkard is well illustrated by this case.

CLINICAL HISTORY

The patient, M. P., a married white man, by occupation a poolroom worker and sailor, had been under treatment in the University of California Hospital in October, 1929, but was transferred to the San Francisco Hospital on November 1st and died there two days later. The clinical history has been summarized by Dr. Cleary.

Complaints on Admission.—Numbness and tingling of the feet of two years' duration, diplopia during the same period of time, and recent inability to walk.

Family History.—Negative.

Past History.—Outside of the present illness of two years' duration the past history was negative, except for irregular mode of living and the history of heavy drinking.

Present Illness.—During the past two years, the patient has noticed occasional numbness and tingling of the lower extremities, most marked after sitting or after lying down and sometimes relieved by rubbing. The symptoms came periodically every two to three weeks and were sometimes accompanied by shooting pains in the extremities and by seeing double for from twenty to thirty minutes.

Five months preceding entry the patient's gait changed; it became of the so-called "slapping" type and he tended to deviate to the left when walking.

According to the wife of the patient, he had of late become drowsy and indifferent, although formerly he was quite active.

Physical Examination.—Florid complexion; obese; irrational at times; unable to move lower limbs. Slight tachycardia, but heart and lungs are essentially negative.

Blood pressure: 141 systolic, 108 diastolic.

The abdomen apparently contained some free fluid, though the signs were not definite. Spleen and liver not palpable.

Neurological Examination.—Deep reflexes entirely lost in the lower extremities and none present in the upper extremities, except the periosteal radials. Babinski signs negative. Hypesthesias (all modalities) on sensory examination of the lower extremities. Edges of optic disks blurred, with mild edema of the disk and a partial filled cup on the right. Horizontal nystagmus noted; diplopia (Dr. Cordes).

Laboratory Examinations.—The blood showed no anemia; there was a slight leukocytosis (11,400). Wassermann negative, in both blood and cerebrospinal fluid. Urine reported as negative.

Course in Hospital.—While in the University of California Hospital the patient became progressively more irrational. On October 28th he became unable to speak and on November 1st he was transferred to the San Francisco Hospital. On admission there, he was wholly irrational and was apparently hallucinating. He continued to be unable to speak. There was cyanosis of the face and lips and the respirations were accelerated to 32 per minute and were shallow. Showers of fine, moist râles could be heard throughout the chest and there was bronchial breathing and slightly diminished resonance at both bases. The pulse was accelerated and was thready.

[1] Clinical-Pathological Conference, San Francisco Hospital, November 26, 1929.

The heart sounds were weak but the heart beat was regular. The white cell count in the blood rose to 28,000 with 92 per cent of polymorphonuclear neutrophils. Supportive treatment was given, but the pulmonary symptoms and signs gradually increased and the patient died on November 3d.

COMMENTS ON THE CLINICAL DATA ACCUMULATED (DR. BARKER)

The case is interesting clinically in that it illustrates the terminal events in a man who has used alcohol to excess over a long period of years. About two years ago signs of involvement of the peripheral nerves appeared (paresthesias and shooting pains in the extremities) and five months before admission a "slapping" gait, suggestive of either peripheral neuritis or of alcoholic pseudotabes, appeared. The areflexia noticeable upon admission was corroborative.

Evidently, psychotic abnormalities had also been appearing for some time since the patient's wife stated that, though formerly active, he had of late become drowsy and indifferent. The diplopia and nystagmus point to lesions either in the eye-muscle nuclei, the motor nerves of the eye, or in the supranuclear paths.

The aphonia that developed in the hospital might have been due either to involvement of the laryngeal nerves or to changes in the nerve centers. The outspoken delirium and hallucinations that developed while in the hospital may have been a part of a delirium tremens because of the withdrawal of alcohol, or may have been due to some other form of alcoholic psychosis, the psychiatric report of the symptoms not being sufficient for differentiation.

The suggestion of fluid within the abdominal cavity points to the possibility of cirrhosis hepatis.

The changes in the lungs during the last few days of life accompanied by consolidation, fever, and polymorphonuclear leukocytosis, point to a terminal drunkard's pneumonia.

One cannot, of course, absolutely rule out an epidemic encephalitis occurring in an alcoholic person, inasmuch as there were disturbances in eye-muscle domains associated with drowsiness and delirium. Against the idea of epidemic encephalitis, however, we have the evidence of changes in the peripheral nerves of at least two years' duration; these had become so marked five months ago that an ataxic gait developed; moreover, the cerebrospinal fluid on examination was reported as entirely negative. It would be interesting here to know whether or not the sugar in this fluid was increased, since hyperglycorrhachia is sometimes the only sign in the spinal fluid in epidemic encephalitis.

On account of the frequency of poliencephalitis superior hemorrhagica in drunkards, it is not impossible that the diplopia and nystagmus may have been due to this.

The most probable clinical diagnoses from the facts accumulated would seem to be the following:

1. Chronic alcoholism.

2. Alcoholic peripheral neuritis, with diminished sensibility in the lower extremities, paresthesias, shooting pains, areflexia, and ataxic gait (alcoholic pseudotabes).

3. Drowsiness, delirium, and hallucination, probably due to wet brain; possibly due, in part, to abstinence after indulgence (psychiatric data reported to me not complete enough to differentiate among delirium tremens, acute alcoholic hallucinosis, and Korsakoff's psychosis).

4. Possibly poliencephalitis superior hemorrhagica of alcoholic origin with eye-muscle paresis, nystagmus, and aphonia.

5. Terminal drunkard's pneumonia with consolidation at both bases, fever, and polymorphonuclear leukocytosis.

SUMMARY OF PATHOLOGIC-ANATOMICAL FINDINGS (DR. BOLIN)

The principal abnormalities found may be summed up as follows:

1. Edema of the pia arachnoid (wet brain; history of alcoholism).
2. Edema of the lungs, bilateral.
3. Bronchopneumonia, bilateral, lower lobes.
4. Dilatation of heart, especially right heart, with soft and flabby heart muscle.
5. Emphysema of lungs, moderate.
6. Fat phanerosis of liver.
7. Obesity.
8. Arteriosclerosis, general, moderate.
9. Pleural adhesions, chronic, fibrous, bilateral.
10. Tattoo marks.

In the microscopical examination of stained sections, the brain was negative except for a moderate distention of the perivascular and perineural spaces; the heart muscle showed edema and stretching apart of the fibers; the kidney showed a mild patchy arteriosclerotic atrophy. With this there was a mild fibrosis of the glomerular tufts.

In view of the fact that the aphonia and the nerve lesions were not reported to us at the time of necropsy, the larynx and the peripheral nerves were not examined.

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THYREO-INTOXICATION WITH NECROSIS AND ATROPHY OF THE LIVER, DAMAGE TO THE HEART MUSCLE AND KIDNEYS, AND TERMINAL BRONCHOPNEUMONIA[1]

WE have long known that the heart, the nervous system, and the genital organs could be injured by the poison in thyreo-intoxication, but it has only recently become clear that the liver also may suffer great damage in the course of Graves' disease. The patient under discussion at the Clinical Pathologic Conference today illustrates exceedingly well this possibility of liver damage in addition to damage to the heart. Prof. Kerr has been especially interested in this association of liver injury with thyreo-intoxication and in connection with Dr. Rusk, he has published a case of acute yellow atrophy of the liver that was associated with hyperthyroidism.

The case that we have now to consider is that of a patient, Annie B., aged sixty-four years, white, a housewife, but widowed, who was admitted to the University of California Hospital on September 7, 1929 and who died the next day.

She was brought into the hospital in coma, and her landlady who had brought her in could give no medical history, except that she had been having *x*-ray treatment to her thyroid gland.

It was subsequently learned from the son of the patient that she had been well until five months before admission, when she began to complain of vague symptoms. She lost weight rapidly, tired easily, and lost her appetite. She soon noticed that her thyroid gland was enlarged and that her eyes were bulging. A friend of the patient, however, reports that she had had goiter for many years and had used iodine solution sometime ago to combat it.

On **physical examination,** the patient though unconscious was extremely restless. Her skin was flushed and of a deep red color, and perspiration was increased. Rectal temperature was 39 C.; rate of respirations 36 per minute; they were deep and noisy and the breath had a fruity odor. The patient's body was markedly emaciated, and the mucous membranes were dry and parched.

The pupils were very small and did not react to light. The eyeballs were soft.

The thyroid gland was enlarged and firm, the right lobe being more prominent than the left. A bruit was audible over the gland but no thrill could be felt. Nothing abnormal was made out in the lungs. The heart was enlarged to the left; the first heart sound was loud and snappy, and a systolic murmur was audible at the apex. There was absolute irregularity in time and in intensity, with a heart rate of 140 per minute (atrial fibrillation). The pulmonic second sound was louder than the aortic second. The volume of the pulse was large. The blood pressure was 170 systolic.

Abdominal examination negative. Deep reflexes hyperactive. Babinski reaction negative on both sides.

On **laboratory examination,** acetone bodies were present in the urine, but without sugar; there was also albuminuria.

As **treatment,** Ringer's solution was given by hypodermoclysis and orange juice was given by nasal tube every two hours. Digalen was administered, at first intra-

[1] Clinical-Pathological Conference at the University of California Medical School, December 12, 1929.

venously and later intramuscularly. The patient also received some Lugol's solution. She showed no signs of improvement, however, and died within twenty-two hours after entry.

CLINICAL DIAGNOSIS

During life the following diagnoses were made:

1. Graves' disease, with vascular struma, tachycardia, exophthalmus, emaciation and hyperhidrosis.
2. Myocardiopathy, with enlargement of the heart, atrial fibrillation, and the possibility of mitral valvular disease.
3. Chronic arterial hypertension (blood pressure 170 systolic).
4. Acidosis, with ketonuria and coma.
5. Probable terminal infection of undetermined source (with fever, tachycardia, and accelerated respiratory rate).

PATHOLOGIC-ANATOMICAL FINDINGS

The chief findings at autopsy were summarized by Dr. Charles L. Connor as follows:

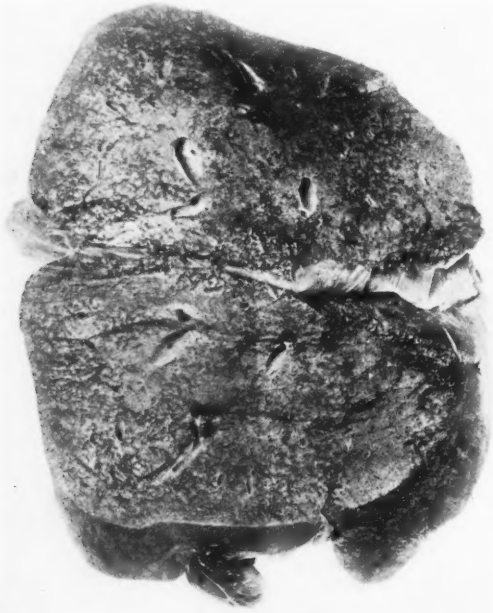

Fig. 45.—U. A., 29, 76. Marked fatty degeneration and necrosis of liver, with associated passive congestion, in case of severe thyrotoxicosis.

1. Diffuse hyperplasia of the thyroid gland, with reduction of colloid and with one adenomatous nodule present; weight of thyroid 80 Gm.
2. Enlargement of the heart (weight 400 Gm.) with evidence of cardiac failure (myocardial insufficiency), but without inflammatory valvular disease.
3. Pulmonary emphysema and beginning bronchopneumonia.
4. Small liver, containing lesions of two kinds: (*a*) Areas of necrosis and (*b*) passive congestion secondary to the cardiac failure (Fig. 45).
5. Tubular degeneration in the kidneys.
6. Early carcinoma of the cervix (in an infantile uterus).
7. Diminished lipoid content of the suprarenal gland.

Here is another interesting case of toxic necrosis of the liver occurring in association with thyreo-intoxication. It would seem to be quite comparable with the areas of toxic necrosis that are met with in the heart muscle in Graves' disease. No signs of luetic or tuberculous infection could be made out.

It is possible that, if it had been suspected *intra vitam*, one might have shown some liver damage by means of liver-function tests (rose bengal test; modified glucose-tolerance test).

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CYSTIC TUMOR OF THE MEDULLA OF THE SUPRARENAL GLAND (PARAGANGLIOMA), ASSOCIATED WITH EARLY AND PERSISTENT ARTERIAL HYPERTENSION, WITH ARTERIAL THICKENING, AND WITH MULTIPLE HEMORRHAGES WITHIN THE CENTRAL NERVOUS SYSTEM, CAUSING EPILEPTIFORM CONVULSIONS, PARALYSES, AND A PSYCHOPATHIC STATE[1]

THIS case is of especial interest inasmuch as the existence of a tumor of the suprarenal medulla was not recognized during life, the patient presenting a history of early and persistent arterial hypertension with evidence of arteriosclerotic changes, of renal damage, and of multiple vascular lesions in the brain.

CLINICAL HISTORY

The patient, P. H., a married man of forty-seven, an accountant, was admitted to the University of California Hospital on September 12, 1929, where he was carefully studied by Professor Kerr and other members of the Medical Staff.

The *chief complaints* were of weakness, disturbance of the mental functions, and recurring convulsions for three months. As a matter of fact, the patient's psyche was too disturbed to permit of reliable answers and the history had to be obtained from his uncle.

Present Illness.—About six months before admission the patient first became aware of a gradual loss of strength and weight, unusual weariness, insomnia, loss of appetite and slight dyspnea on exertion. Three months later he suffered an epileptiform attack, characterized by a groan followed by loss of consciousness, frothing at the mouth, urinary incontinence, and tonic contraction of the right side of the body. He fell during this attack, fractured his left humerus, and was taken to the Berkeley General Hospital. During the first night there he had several convulsions; one of these lasted seven hours, and in it the respirations fell to 6 per minute. During the subsequent three weeks the convulsive seizures disappeared; they were not followed by paralysis. The mind of the patient seemed to be affected however; he became disoriented and hallucinations and delusions were manifest. He was said to be too ill to permit of adequate treatment of his fracture.

One month before entry to the University of California Hospital, convulsive seizures returned and he became weaker. There was no nausea, vomiting, headache, visual disturbance, or edema of the extremities.

Previous History.—Except for a vague history of "spasms" in childhood, the previous history throws but little light upon the case. He is said to have had tonsillitis in early life. His habits have been temperate, and his disposition steady and calm.

Physical Examination.—Undernourished, coarse tremor of lips and hands, mentally disoriented. Right pupil larger than the left. Pupillary reactions sluggish. Blurred disk margin in right eye; sclerosis of retinal vessels; a few minute hemorrhages, and several areas of exudate. Left fundus similar to right. Slight weakness of left face. Coarse tremor of tongue. Enlargement of heart to both right and left, with heaving of whole precordium. Soft systolic murmur; aortic second sound accentuated; thickened peripheral arteries; pulse rate 90. Blood pressure, 200 systolic, 114 diastolic.

Liver edge 3 cm. below the costal margin. Spleen not palpable.

[1] Clinical-Pathological Conference at the University of California Medical School, December 5, 1929.

Coarse tremor of hands; deformity of left shoulder following fracture. Hyperactive deep reflexes, more marked on the left than on the right. Suggestive Babinski on the left. Abdominal and cremasteric reflexes normal.

Laboratory Tests.—*Blood.*—Practically normal. *Urine:* Contains a trace of albumin and many hyaline and coarsely granular casts. The phthalein output was 45 per cent in two hours. *Cerebrospinal fluid:* Negative.

Test of renal function (Mosenthal's method) showed a tendency to fixation of the specific gravity between 1.009 and 1.013. Day urine, 711 cc.; night urine, 575 cc.

***x*-Ray Examinations.**—*Skull* showed a calcified pineal gland, and a partially closed in sella turcica. *Chest* negative. Old fracture of *left humerus*, with deformity.

Course in the Hospital.—The patient was placed upon a diet low in salt and low in protein, and glucose was given intravenously. He also received digitalis leaves and caffeine, but he failed rapidly, the weakness increased, and he became stuporous and irrational. During the last few days and nights of his life the temperature rose, owing to a terminal infection. He died upon the eleventh day of residence in the hospital.

PATHOLOGIC-ANATOMICAL FINDINGS (DR. CONNOR)

At the autopsy, made by Dr. Charles Earl Connor, the principal findings were as follows:

1. Tumor of the medulla of the left suprarenal capsule (cystic and broken down), with a thin layer of cortex over it, and containing cells with an affinity for chrome salts (Fig. 46).

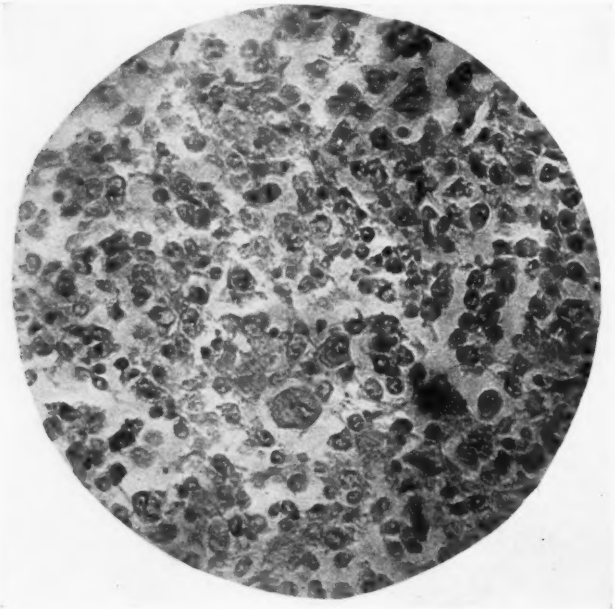

Fig. 46.—U. A., 29, 80. Tumor of suprarenal medulla (immature chromaffin cells). Photomicrograph × 400.

2. Generalized arteriosclerosis.

3. Red granular kidneys with some contraction (arteriolar nephropathy).

4. Multiple vascular lesions of the brain, including an infarction of the right frontal lobe, old and recent hemorrhage in the cerebral peduncles, more marked on the left than on the right, hemorrhage in the upper part of the pons in the region of the eye-muscle nuclei, and hemorrhage at the upper end of the fourth ventricle.

5. Old fracture of the left humerus with deformity.

6. Terminal bronchopneumonia.

THE OCCURRENCE OF TUMORS IN THE SUPRARENAL MEDULLA

Dr. Connor tells me that he has observed three of these tumors and other cases were reported by Oppenheimer and Fishberg in the *Archives of Internal Medicine* for 1924.

These tumors have been believed to be very rare, but it is possible that they would be discovered much oftener if they were systematically looked for.

Several types of tumor of the suprarenal medulla have been described: (1) *Paraganglioma of the chromaffine system* is a pure, sympathetic tumor. (2) *Ganglioneuroma* contains ganglion cells and nonmedullated nerve fibers. (3) *Neuroblastoma* consists chiefly of sympathetic cells, but it exhibits malignancy, since there are frequently metastases in the liver and the tumors contain large, atypical, sarcoma-like cells. Still other forms of tumor, including glioma, have been described. Hedinger mentions a cystic medullary struma of the suprarenal.

In the case of paraganglioma described by Wichels and Biebl, the symptoms were not unlike those presented by the patient under discussion today. They found bilateral tumors of the suprarenal medulla in a man of thirty-six who had arterial hypertension, multiple brain hemorrhages, and glycosuria.

In one case described by French writers (Labbé, Pinel, and Doumer), a paraganglioma was found in the left kidney; it consisted of cells like those of the suprarenal medulla. Their patient was a woman of twenty-eight who had had attacks of nausea and vomiting, with vasomotor disturbances, and with crises of arterial hypertension. These crises began with a chilly feeling and pallor of the skin, after which there was subjective palpitation, tachycardia, and sweating; the extremities became cold and cyanotic, and the patient developed albuminuria, fever, and a further increase of the blood pressure. Death occurred from pulmonary edema.

Can *hyperplasia* of the suprarenal medulla or of the chromaffine system in general be held responsible for arterial hypertension in the absence of suprarenal tumor?

Since Wiesel suggested that arterial hypertension is due to an over-

function of the chromaffine system, many articles upon the subject have appeared. Wiesel studied 22 cases of chronic renal disease and some cases of acute renal disease, all of which showed hypertrophy of the heart, and in these cases at autopsy he found hyperplasia of the chromaffine tissue, not only in the medulla of the suprarenals, but also in the paraganglia. He and his colleagues later attempted to demonstrate an increase of epinephrine in the blood serum and similar attempts have been made by other investigators. The tests for epinephrine in the blood serum are, however, not very satisfactory, even when the frog's eye, strips of cat's intestine, or strips of rabbit's uterus are used as test objects. Some maintain that there is no increase of epinephrine in the blood but, instead, an increased excitability of the vessels, dependent, perhaps, upon substances like peptone.

Injection of epinephrine into rabbits over long periods gives rise to disease of the media of the blood vessels and sometimes to sclerosis. In patients with tumors of the suprarenal medulla, the vascular changes are said to be chiefly alterations of the tunica media. However, Braun was able through intravenous injection of small doses of epinephrine to cause arteriosclerotic changes of the small vessels, as well as heart hypertrophy. All investigators agree, however, that arteriosclerosis of larger arteries without increase of blood pressure is not related to disturbances of the functions of the chromaffine tissue, for, in such cases, the primary degeneration involves the elastic elements. The whole matter must still be considered to be *sub judice;* further investigations will be necessary before any definite decision can be reached.

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AN EXTRAORDINARY GENITO-SUPRARENAL SYNDROME (ADULT FORM OF HYPERINTERRENOPATHY WITH VIRILISM AND HIRSUTISM) DUE TO MALIGNANT TUMOR ORIGINATING IN THE CORTEX OF THE RIGHT SUPRARENAL GLAND; AUTOPSY FINDINGS[1]

DR. W. J. KERR: As Dr. Hans Lisser has some excellent lantern slides of the patient and is thoroughly familiar with the history of the case, I shall ask him to give us a summary of the clinical findings and of the diagnosis that was made during life.

CLINICAL HISTORY

DR. HANS LISSER: The patient, an Italian woman of thirty-eight, was admitted to this hospital on January 11, 1926.

Fig. 47.—U. A., 26, 46. Same patient as Fig. 48, as she appeared before onset of symptoms due to a tumor (carcinoma) originating in cortex of suprarenal.

Her *chief complaints* were of dull pain in the right side of the abdomen and back, abnormal growth of hair over the body, and abrupt cessation of menstruation.

Of her **past history,** it was learned that she had lived in Italy until twenty-three years of age, since when she had lived in California. She had married at twenty-four and had passed through four normal pregnancies. Her appendix was removed at twenty-eight and her tonsils at twenty-nine. At thirty-five she underwent an anterior and posterior colporrhaphy. Otherwise, except for a tendency to insomnia, she seems to have been well up to the time of onset of the present illness. A photograph of the patient at the age of thirty-five (Fig. 47) shows that she was then of normal external appearance.

[1] Clinical-Pathological Conference, Cole Hall, University of California Medical School, December 5, 1929.

Fig. 48.—U. A., 26, 46. Case of carcinoma originating in suprarenal cortex with virilism. Note mustache and beard. Compare with Fig. 47 when patient was two years younger (Lisser).

Fig. 49.—U. A., 26, 46. Same patient as Fig. 47. Note heavy growth of hair on cheeks and chin (Lisser).

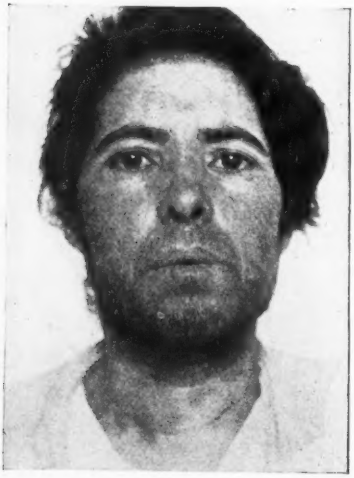
The **present illness**, as recorded in the hospital record, began two years before admission with frequent attacks of sharp pain in the right lumbar region. These

pains during the six months preceding admission had become "bearing-down" in type. Some fifteen months before admission, she noticed a rapid growth of hair on her face, trunk, and extremities. Menstruation, which had shown no earlier abnormalities, ceased abruptly nine months before entry to the hospital and there had been no "show" since, save a slight serous discharge lasting but one day at the end of the first month of amenorrhea. For four months before entry to the hospital she had had hot flushes. During the past two years, sexual frigidity had developed. For over nine months there had been gradual loss of weight (19 pounds). For some four months, she had noticed a gradual darkening of the color of her skin. During this latter period, she had profuse night sweats, her appetite grew poorer and she became gradually weaker.

Fig. 50.—U. A., 26, 46. Same patient as Fig. 47. Note heavy hair growth on thighs and crines pubes of masculine type, hirsutismus, heterosexual hair distribution (Lisser).

On **physical examination,** her features, particularly the lines of her face, suggested the masculine type. There was a heavy growth of dark coarse hairs over her face (outspoken beard, Figs. 48, 49), and a large amount of hair over the arms and legs, this growth being especially marked over her thighs (Fig. 50). The pubic hair conformed to the masculine type of distribution ("triangular crines"). The skin of the body had become deeply pigmented (of a dark brown color), but this pigment was absent in the folds of the skin; there was some pigmentation of the palms of the hands. The skin was coarse in texture. The breasts were large and pendulous and there was marked hypertrophy of the clitoris (Fig. 51).

In the abdomen, the spleen was not palpable, but the liver edge could be felt just below the right costal margin. A tumor mass measuring 9 x 5 cm. could be felt



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The **present illness**, as recorded in the hospital record, began two years before admission with frequent attacks of sharp pain in the right lumbar region. These

pains during the six months preceding admission had become "bearing-down" in type. Some fifteen months before admission, she noticed a rapid growth of hair on her face, trunk, and extremities. Menstruation, which had shown no earlier abnormalities, ceased abruptly nine months before entry to the hospital and there had been no "show" since, save a slight serous discharge lasting but one day at the end of the first month of amenorrhea. For four months before entry to the hospital she had had hot flushes. During the past two years, sexual frigidity had developed. For over nine months there had been gradual loss of weight (19 pounds). For some four months, she had noticed a gradual darkening of the color of her skin. During this latter period, she had profuse night sweats, her appetite grew poorer and she became gradually weaker.

Fig. 50.—U. A., 26, 46. Same patient as Fig. 47. Note heavy hair growth on thighs and crines pubes of masculine type, hirsutismus, heterosexual hair distribution (Lisser).

On **physical examination,** her features, particularly the lines of her face, suggested the masculine type. There was a heavy growth of dark coarse hairs over her face (outspoken beard, Figs. 48, 49), and a large amount of hair over the arms and legs, this growth being especially marked over her thighs (Fig. 50). The pubic hair conformed to the masculine type of distribution ("triangular crines"). The skin of the body had become deeply pigmented (of a dark brown color), but this pigment was absent in the folds of the skin; there was some pigmentation of the palms of the hands. The skin was coarse in texture. The breasts were large and pendulous and there was marked hypertrophy of the clitoris (Fig. 51).

In the abdomen, the spleen was not palpable, but the liver edge could be felt just below the right costal margin. A tumor mass measuring 9 x 5 cm. could be felt

on deep palpation to the right of the median line just above the level of the umbilicus; it was firm, slightly tender, and movable in all directions. There were no signs of fluid in the abdominal cavity. The superficial veins in both lumbar regions and in both lower abdominal quadrants were somewhat dilated. Rectal and pelvic examinations negative. All reflexes were normal. Lungs and heart were negative.

Laboratory Examinations.—*Blood.*—Red blood cells, 4,144,000; hemoglobin, 78 per cent (Sahli); white blood cells, 13,800; differential count showed polymorphonuclear neutrophil leukocytes, 75 per cent; small morphonuclears, 16 per cent; large morphonuclears, 9 per cent. Wassermann negative.

The *urine* contained a trace of albumin and a few pus cells and some motile rods, shown by culture to be *Bacillus coli*. The phthalein output was 30 per cent in two hours. The Mosenthal test revealed 350 cc. of night urine, 600 cc. of day urine, with a specific gravity varying between 1.020 and 1.025; no sugar or bile present.

Fig. 51.—U. A., 26, 46. Enlarged clitoris of patient shown in Fig. 50. Amenorrhea since eight months, previously regular and normal, hot flushes for four months.

On examining the *blood chemistry*, the blood sugar was 98 mg. per cent, the non-protein nitrogen 38.4 mg. per cent and the uric acid 3.5 mg. per cent—all within normal limits.

On **roentgenological examination**, the structures within the chest were negative and the skull was normal. Pyelograms showed that the right kidney was low, that its pelvis was slightly dilated, and that the upper calyx of the latter was flattened. In the gastro-intestinal series, the stomach was displaced to the left by the mass in the right abdomen, as was the gallbladder in the cholecystographic films. On *x*-ray, after injection of air into the peritoneal cavity, the shadow due to the right kidney and that due to the liver appeared to be continuous, but these structures could not be sharply outlined.

The **diagnosis of tumor originating in the cortex of the right suprarenal gland** was made on the basis of the palpatory findings and

the extraordinary virilism and hirsutism that had so rapidly developed. We discussed whether to resort to surgical therapy or to be content with deep *x*-ray treatment. After consultations with Drs. Kerr and Terry, exploratory laparotomy was decided upon, and the operation was undertaken by Dr. Terry. There was much bleeding and the patient showed so much shock that attempts at removal of the tumor had to be abandoned. Despite the administration of intravenous glucose and a blood transfusion, the patient died in the operating room.

(Dr. Lisser then threw upon the screen also some slides illustrating pseudohermaphroditism and premature puberty, due to overactivity of the suprarenal cortex before birth and during childhood, respectively.)

DR. KERR: We had hoped, since the mass had been freely movable, that it might be possible to excise the tumor, since had it been possible to do this successfully, the outlook for the patient would have been better than by *x*-ray therapy. I should be glad if Dr. Barker would comment upon the justifiability of the diagnosis made in this case.

DR. BARKER: One seldom meets with a case history of greater clinical interest than this. I spent a part of last evening going over the clinical notes recorded upon the case, and I jotted down as follows the diagnostic inferences that the data, as accumulated, seemed to me to justify:

1. Genito-suprarenal syndrome (late, or adult form of postnatal hyperinterrenopathy), with virilism and hirsutism, associated with the presence of a tumor mass that was palpable in the upper right abdomen, almost certainly a tumor that had originated in the right suprarenal cortex. The pigmentation of the skin and the asthenia may possibly have been due to secondary involvement of the suprarenal medulla from pressure (though the blood pressure was not very low, 120 systolic, 65 diastolic).

2. Residuals of coli-bacilluric infection of the urinary tract (pyuria, *Bacilli coli* in the urine, dilatation of the right renal pelvis) with evidence of distortion of the upper calyx from pressure and with a history of treatment for pyelitis that was accompanied by chills, high fever, and sweats.

3. Dilated venules in both lumbar regions and in both lower quadrants of the abdomen, possibly indicating obstruction to the vena cava with beginning development of a collateral circulation between the inferior and the superior cava.

4. Mild secondary anemia (red blood cells, 4,144,000; hemoglobin, 78 per cent Sahli), with slight polymorphonuclear leukocytosis (due to infection?).

5. Early and abrupt menopause (at the age of thirty-seven) with hot flushes and sexual frigidity (possibly related to the developing virilism, since dystrophy of the ovaries has sometimes been observed in association with virilism).

6. Slightly accelerated basal metabolic rate (17.2 per cent +), possibly indicating a secondary slight overactivity of the thyroid gland, though there was no struma nor any other sign of hyperthyroidism (pulse rate 80).

You will find an admirable summary of our knowledge of suprarenal endocrine disorders in Dr. Lisser's recent article in Blumer's *Bedside Diagnosis*. On reading it yesterday, I was glad to see that he made mention of this case that we are discussing today.

The tissue making up the cortex of the suprarenal gland corresponds to the interrenal system of animals, whereas the medulla of the suprarenal is a part of the chromaffine system; accordingly it is convenient to designate the diseases of the cortex as "interrenopathies" and the diseases of the medulla as "chromaffinopathies," making use of the prefixes "hyper" and "hypo" for overactivity and underactivity, respectively, just as we do with the other endocrine glands.

I am eager to hear of the autopsy findings.

SUMMARY OF THE FINDINGS AT AUTOPSY (DR. CHARLES L. CONNOR)

1. Carcinoma of the right adrenal cortex with direct infiltration into the inferior cava and complete blockage of it from the diaphragm (above this no examination was made) down to the pelvic veins (Figs. 52–54).

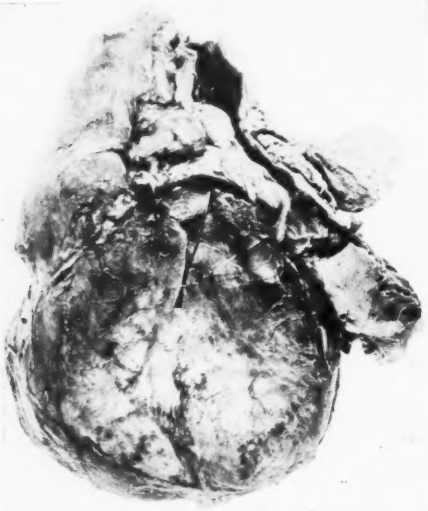

Fig. 52.—U. A., 26, 46. Carcinoma originating in suprarenal cortex removed from patient shown in Figs. 47–51.

Fig. 53.—U. A., 26, 46. Cross section of tumor shown in Fig. 52. Carcinoma originating in suprarenal cortex.

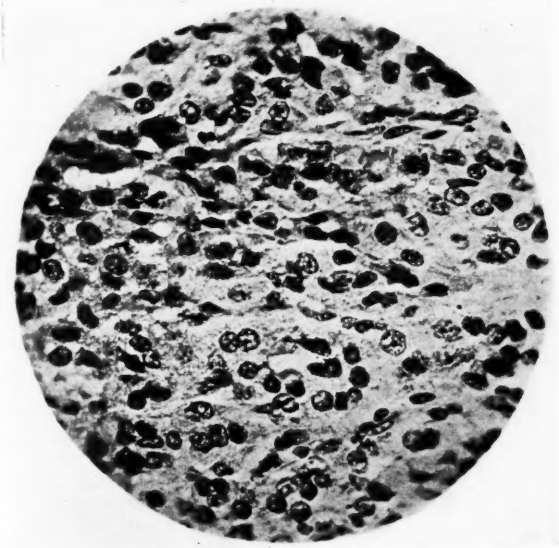

Fig. 54.—U. A., 26, 46. Photomicrograph showing cell details of tumor in Fig. 53. Carcinoma originating in suprarenal cortex (× 400).

2. Marked hypertrichosis with male distribution of hair.
3. Markedly hypertrophied clitoris.
4. Decidual reaction (?) with focal abscesses in the uterine mucosa. Involutional changes in ovaries.
5. Hemoperitoneum (1 liter of unclotted blood).
6. Unhealed laparotomy wound with gauze drain from one end.

FURTHER DISCUSSION

DR. KERR: I feel that the findings in this case clearly show the possibility of making the positive diagnosis, in certain instances at least, of tumor originating in the suprarenal cortex. I have wondered how the patient would have got along had it been possible to remove successfully the tumor at an earlier stage. As we learn from the autopsy report, operation was undertaken at too late a time, even if the patient had survived removal of the mass, since, though there were no metastases at a distance, the tumor had already grown into the renal vein and the vena cava.

DR. LISSER: It has occurred to me that the weakness and the mild acceleration of the basal metabolic rate in this patient may have been due to the neoplasm itself.

Cases of hirsutism are very common, especially in their milder forms, and if we could find some effective method of treatment of the milder forms, it would rejoice the hearts of many women. Of course, women object to hair on their faces. When there are only a few, they can go to the dermatologist for treatment by electrolysis; but when there is a coarse and heavy beard such as this patient exhibited, treatment by electrolysis is a hopeless undertaking.

In a case reported by Gordon Holmes in the *Quarterly Journal of Medicine* (1925), a girl formerly very attractive physically, developed a heavy beard and general hypertrichosis due to the slow growth of a tumor starting in the cortex of the right suprarenal. Her features changed so as strongly to suggest those of a male. Menstruation ceased, the clitoris hypertrophied, and she lost all interest in the opposite sex and preferred the society of women. The right suprarenal was removed and all the symptoms of virilism disappeared. Menstruation reappeared and became regular, the clitoris returned to its normal size, the abnormal hair began to fall out soon after the operation and, later, disappeared entirely. There was some falling out of the hair of the scalp but it grew again. The breasts developed and, in general, femininity reappeared. Nine years after the operation, the patient seemed to be, in every respect, still a perfectly normal woman! A result such as this would certainly seem to make it worth while for the victim of suprarenal virilism to brave the risks of surgical interference.

DR. BARKER: Anything that is detrimental to the physical health

and beauty, or to the mental and emotional states, of our patients should enlist our interest as physicians. It is perfectly true that hairs on the chin or on the upper lip can be very disturbing to a sensitive woman. If there are only a few, they will pluck them out themselves with pincers before a mirror; if there are more, the dermatologist may help them by electrolysis or by *x*-ray treatment. But where there is a coarse beard such as the patient under discussion had, the only cure lies in timely removal of the suprarenal tumor, or in mitigation of the symptoms, possibly by deep roentgenotherapy. The cure in Gordon Holmes case (referred to by Dr. Lisser) by removal of the tumor was truly marvelous.

When I was in India in 1899, a medical missionary there, Dr. Margaret Mackellar told me that she had seen large numbers of cases of premature puberty among the native girls. Whether the onset of puberty in these girls before the age of four, six, or eight was due in any way to climatic influences, she did not know.

I recall once seeing a little girl of eight in Charlotte, North Carolina, who had menstruated since infancy and had developed all the secondary sex characters; except for this sexual prematurity she seemed to be a healthy child.

The cases of premature puberty are apparently not always due to disease of the suprarenal cortex. In Dr. Howard Kelly's clinic I saw a girl of seven whose pubertas praecox was associated with the presence of a large ovarian tumor. It has long been known, too, that tumors (especially teratomata) of the pineal gland or of its neighborhood may be accompanied by premature puberty. For a time it was supposed that the phenemona were due to a disturbance of the endocrine functions of the pineal (hyperpinealism), but it now seems more likely that they must be due to involvement of the higher centers of the vegetative nervous system. It is a remarkable thing that almost all the classical endocrinopathies may be aped by the symptoms that may follow upon lesions in different parts of the hypothalamus.

There is one matter of more theoretical than practical interest that perhaps Dr. Connor would be willing to comment upon. When I was working at pathologic anatomy—a good many years ago, now—we assumed that carcinoma developed primarily only in tissues of ectodermal or endodermal origin, not in those of mesodermal derivation. Embryologists usually described the interrenal system (cortex of the suprarenal) as of mesodermal origin. Is it really not mesodermal in origin, or have the views of pathologists been altered so as to admit that a primary carcinoma may originate in mesodermal tissue?

Dr. Connor: It seems to be generally admitted now by pathologic anatomists and histologists that true carcinomata may develop (as primary growths) in tissues of mesodermal origin, for example, in the kidneys as well as in the suprarenals.

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